```
Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  DEC 05  CASREACT(R) - Over 10 million reactions available
 NEWS  4  DEC 14  2006 MeSH terms loaded in MEDLINE/LMEDLINE
 NEWS  5  DEC 14  2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
 NEWS  6  DEC 14  CA/CAplus to be enhanced with updated IPC codes
 NEWS  7  DEC 21  IPC search and display fields enhanced in CA/CAplus with the
                  IPC reform
 NEWS  8  DEC 23  New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                  USPAT2
 NEWS  9  JAN 13  IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS 10  JAN 13  New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                  INPADOC
 NEWS 11  JAN 17  Pre-1988 INPI data added to MARPAT
 NEWS 12  JAN 17  IPC 8 in the WPI family of databases including WPIFV

 NEWS EXPRESS  JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
               V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
               http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
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  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:38:24 ON 23 JAN 2006

=> file dissab
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21

FILE 'DISSABS' ENTERED AT 10:38:39 ON 23 JAN 2006
COPYRIGHT (C) 2006 ProQuest Information and Learning Company; All Rights Reserved.
```

FILE COVERS 1861 TO 20 DEC 2005 (20051220/ED)


```
=> s melanin
           261 MELANIN
            20 MELANINS
L1         267 MELANIN
                (MELANIN OR MELANINS)

=> s 6D2
L2           1 6D2

=> s l2 and l1
L3           1 L2 AND L1

=> d ibib 1
```

L3 ANSWER 1 OF 1 DISSABS COPYRIGHT (C) 2006 ProQuest Information and Learning Company; All Rights Reserved on STN

ACCESSION NUMBER:	2005:39050 DISSABS Order Number: AAI3155910
TITLE:	Function and secretion of Cryptococcus neoformans virulence factors glucuronoxylomannan and laccase
AUTHOR:	Garcia Rivera, Javier [Ph.D.]; Casadevall, Arturo [advisor]
CORPORATE SOURCE:	Yeshiva University (0266)
SOURCE:	Dissertation Abstracts International, (2005) Vol. 65, No. 12B, p. 6175. Order No.: AAI3155910. 162 pages. ISBN: 0-496-16470-8.
DOCUMENT TYPE:	Dissertation
FILE SEGMENT:	DAI
LANGUAGE:	English
ENTRY DATE:	Entered STN: 20050826 Last Updated on STN: 20050826

```
=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y
```

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.66	1.87

```
STN INTERNATIONAL LOGOFF AT 10:39:24 ON 23 JAN 2006


Connection closed by remote host
```

```
Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
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 NEWS  6  DEC 14  CA/CAplus to be enhanced with updated IPC codes
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                  IPC reform
 NEWS  8  DEC 23  New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                  USPAT2
 NEWS  9  JAN 13  IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS 10  JAN 13  New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                  INPADOC
 NEWS 11  JAN 17  Pre-1988 INPI data added to MARPAT
 NEWS 12  JAN 17  IPC 8 in the WPI family of databases including WPIFV

 NEWS EXPRESS  JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,
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               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
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               http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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Enter NEWS followed by the item number or name to see news on that
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  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
```

```
 FILE LAST UPDATED: 21 JAN 2006 (20060121/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 will soon be available.  For details
 on the 2005 reload, enter HELP RLOAD at an arrow promt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate

=> s melanin
          7148 MELANIN
          6333 MELANINS
L1        9970 MELANIN
                 (MELANIN OR MELANINS)

=> s melanoma
         60502 MELANOMA
          9282 MELANOMAS
            80 MELANOMATA
             1 MELANOMATAS
L2       61483 MELANOMA
                 (MELANOMA OR MELANOMAS OR MELANOMATA OR MELANOMATAS)

=> s l2 and l1
L3        2328 L2 AND L1

=> s antibod?
L4      705098 ANTIBOD?

=> s l3 and l4
L5         198 L3 AND L4

=> s anti (W2) melanin
MISSING OPERATOR 'ANTI (W2'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s anti (N2) melanin
MISSING OPERATOR 'ANTI (N2'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s anti (2w) melanin
        589948 ANTI
             6 ANTIS
        589952 ANTI
                 (ANTI OR ANTIS)
          7148 MELANIN
          6333 MELANINS
          9970 MELANIN
                 (MELANIN OR MELANINS)
L6           7 ANTI (2W) MELANIN
```

```
=> s l6 and l2
L7            2 L6 AND L2

=> d ibib 1-2

L7   ANSWER 1 OF 2     MEDLINE on STN
ACCESSION NUMBER:    92335128     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 1631018
TITLE:               Response of transformed and normal mouse cell lines to
                     anti-melanin compounds, hyperthermia, and
                     radiation.
AUTHOR:              Raaphorst G P; Azzam E I
CORPORATE SOURCE:    Ottawa Regional Cancer Centre, Ontario, Canada.
SOURCE:              Pigment cell research / sponsored by the European Society
                     for Pigment Cell Research and the International Pigment
                     Cell Society, (1992 Feb) 5 (1) 25-9.
                     Journal code: 8800247. ISSN: 0893-5785.
PUB. COUNTRY:        Denmark
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199208
ENTRY DATE:          Entered STN: 19920904
                     Last Updated on STN: 19970203
                     Entered Medline: 19920820

L7   ANSWER 2 OF 2     MEDLINE on STN
ACCESSION NUMBER:    88107389     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 3426925
TITLE:               Radiation, heat and anti-melanin drug
                     response of a transformed mouse embryo cell line with
                     varying melanin content.
AUTHOR:              Raaphorst G P; Azzam E I
CORPORATE SOURCE:    Ottawa Regional Cancer Center, Ontario, Canada.
SOURCE:              British journal of cancer, (1987 Nov) 56 (5) 622-4.
                     Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY:        ENGLAND: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         198803
ENTRY DATE:          Entered STN: 19900305
                     Last Updated on STN: 19900305
                     Entered Medline: 19880309


=> s l7 and l4
L8            0 L7 AND L4

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                1.90       2.11

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1907 - 23 Jan 2006 VOL 144 ISS 5
FILE LAST UPDATED: 22 Jan 2006 (20060122/ED)


```
=> s melanin
          9775 MELANIN
          7167 MELANINS
L9       11188 MELANIN
                (MELANIN OR MELANINS)

=> s cancer or tumor or neoplas? or melanoma?
        267591 CANCER
         38666 CANCERS
        277754 CANCER
                (CANCER OR CANCERS)
        359426 TUMOR
        142769 TUMORS
        405092 TUMOR
                (TUMOR OR TUMORS)
        435881 NEOPLAS?
         30616 MELANOMA?
L10     690010 CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?

=> s l9 (l) l10
L11       1762 L9 (L) L10

=> s antibod?
L12     451938 ANTIBOD?

=> s l11 and l12
L13         60 L11 AND L12

=> s l3 (l) l9
PROXIMITY OPERATION NOT ALLOWED
Certain operators may not be nested in combination with other
operators.  A nested operator is valid only when it occurs at the same
level or above the operator outside the nested phrase as determined by
the following precedence list:

                    1.    Numeric
                    2.    (W), (NOTW), (A), (NOTA)
                    3.    (S), (NOTS)
                    4.    (P), (NOTP)
                    5.    (L), (NOTL)
                    6.    AND, NOT
                    7.    OR

For example, '(MONOCLONAL(W)ANTIBOD?)(L)ANTIGEN?' is valid since (W)
is above (L) on the precedence list.  However,
'((THIN(W)LAYER)(L)PHOSPHOLIPID#)(A)LACTONE#' is not valid since (L)
is below (A) on the precedence list.  The only exception is the 'OR'
operator.  This operator may be used in combination with any other
operator.  For example, '(ATOMIC OR NUCLEAR)(W)REACTOR' is valid.
```

```
=> s l9 (l) l12
L14         190 L9 (L) L12

=> s l14 and l10
L15          59 L14 AND L10

=> s l14 and l13
L16          53 L14 AND L13

=> s l16 not py>2002
       3463589 PY>2002
L17          45 L16 NOT PY>2002

=> d ibib 1-3

L17  ANSWER 1 OF 45  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2001:711229  CAPLUS
DOCUMENT NUMBER:          136:4079
TITLE:                    Abnormal translocation of tyrosinase and
                          tyrosinase-related protein 1 in cutaneous melanocytes
                          of Hermansky-Pudlak syndrome and in melanoma cells
                          transfected with anti-sense HPS1 cDNA
AUTHOR(S):                Sarangarajan, Rangaprasad; Budev, Ashish; Zhao, Yang;
                          Gahl, William A.; Boissy, Raymond E.
CORPORATE SOURCE:         Department of Dermatology, University of Cincinnati,
                          Cincinnati, OH, USA
SOURCE:                   Journal of Investigative Dermatology (2001), 117(3),
                          641-646
                          CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER:                Blackwell Science, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          12    THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17  ANSWER 2 OF 45  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2000:597655  CAPLUS
DOCUMENT NUMBER:          133:249026
TITLE:                    Studies on epidermis reconstructed with and without
                          melanocytes: melanocytes prevent sunburn cell
                          formation but not appearance of DNA damaged cells in
                          fair-skinned caucasians
AUTHOR(S):                Cario-Andre, Muriel; Pain, Catherine; Gall, Yvon;
                          Ginestar, Jose; Nikaido, Osamu; Taieb, Alain
CORPORATE SOURCE:         Unite de Dermatologie, Universite Victor Segalen
                          Bordeaux II, Bordeaux, 33076, Fr.
SOURCE:                   Journal of Investigative Dermatology (2000), 115(2),
                          193-199
                          CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER:                Blackwell Science, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          45    THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17  ANSWER 3 OF 45  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2000:380955  CAPLUS
DOCUMENT NUMBER:          134:39063
TITLE:                    T311 - an anti-tyrosinase monoclonal antibody
                          for the detection of melanocytic lesions in paraffin
                          embedded tissues
AUTHOR(S):                Jungbluth, Achim A.; Iversen, Kristin; Coplan, Keren;
                          Kolb, Denise; Stockert, Elisabeth; Chen, Yao-Tseng;
                          Old, Lloyd J.; Busam, Klaus
```

```
CORPORATE SOURCE:        Ludwig Institute for Cancer Research at Memorial
                         Sloan-Kettering Cancer, New York, NY, 10021, USA
SOURCE:                  Pathology, Research and Practice (2000), 196(4),
                         235-242
                         CODEN: PARPDS; ISSN: 0344-0338
PUBLISHER:               Urban & Fischer Verlag
DOCUMENT TYPE:           Journal
LANGUAGE:                English
REFERENCE COUNT:         45    THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d his

     (FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

     FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1          9970 S MELANIN
L2         61483 S MELANOMA
L3          2328 S L2 AND L1
L4        705098 S ANTIBOD?
L5           198 S L3 AND L4
L6             7 S ANTI (2W) MELANIN
L7             2 S L6 AND L2
L8             0 S L7 AND L4

     FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9         11188 S MELANIN
L10       690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11         1762 S L9 (L) L10
L12       451938 S ANTIBOD?
L13           60 S L11 AND L12
L14          190 S L9 (L) L12
L15           59 S L14 AND L10
L16           53 S L14 AND L13
L17           45 S L16 NOT PY>2002

=> s in vivo
         413660 VIVO
              2 VIVOS
L18      413661 IN VIVO
                   (VIVO OR VIVOS)

=> s l18 and l17
L19           3 L18 AND L17

=> d ibib 1-3

L19  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2000:597655  CAPLUS
DOCUMENT NUMBER:         133:249026
TITLE:                   Studies on epidermis reconstructed with and without
                         melanocytes: melanocytes prevent sunburn cell
                         formation but not appearance of DNA damaged cells in
                         fair-skinned caucasians
AUTHOR(S):               Cario-Andre, Muriel; Pain, Catherine; Gall, Yvon;
                         Ginestar, Jose; Nikaido, Osamu; Taieb, Alain
CORPORATE SOURCE:        Unite de Dermatologie, Universite Victor Segalen
                         Bordeaux II, Bordeaux, 33076, Fr.
SOURCE:                  Journal of Investigative Dermatology (2000), 115(2),
                         193-199
                         CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER:               Blackwell Science, Inc.
DOCUMENT TYPE:           Journal
```

LANGUAGE: English
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:304007 CAPLUS
DOCUMENT NUMBER: 134:191455
TITLE: gp100 mRNA is more sensitive than tyrosinase mRNA for RT-PCR amplification to detect circulating melanoma cells in peripheral blood of melanoma patients
AUTHOR(S): Tsukamoto, K.; Ueda, M.; Hirata, S.; Osada, A.; Kitamura, R.; Takahashi, T.; Ichihashi, M.; Shimada, S.
CORPORATE SOURCE: Nakakoma, Tamaho, 1110 Shimokato, Department of Dermatology, Yamanashi Medical University, Yamanashi, Japan
SOURCE: Journal of Dermatological Science (2000), 23(2), 126-131
CODEN: JDSCEI; ISSN: 0923-1811
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:143024 CAPLUS
DOCUMENT NUMBER: 108:143024
TITLE: Cyclic AMP induces differentiation in vitro of human melanoma cells
AUTHOR(S): Giuffre, Laura; Schreyer, Magali; Mach, Jean Pierre; Carrel, Stefan
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Epalinges, CH-1066, Switz.
SOURCE: Cancer (New York, NY, United States) (1988), 61(6), 1132-41
CODEN: CANCAR; ISSN: 0008-543X
DOCUMENT TYPE: Journal
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1 9970 S MELANIN
L2 61483 S MELANOMA
L3 2328 S L2 AND L1
L4 705098 S ANTIBOD?
L5 198 S L3 AND L4
L6 7 S ANTI (2W) MELANIN
L7 2 S L6 AND L2
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9 11188 S MELANIN
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11 1762 S L9 (L) L10
L12 451938 S ANTIBOD?
L13 60 S L11 AND L12
L14 190 S L9 (L) L12
L15 59 S L14 AND L10
L16 53 S L14 AND L13
L17 45 S L16 NOT PY>2002

```
L18      413661 S IN VIVO
L19           3 S L18 AND L17

=> s l17 and label?
        426929 LABEL?
L20           4 L17 AND LABEL?

=> d ibib 1-4

L20  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1998:426503  CAPLUS
DOCUMENT NUMBER:          129:201389
TITLE:                    Comparative immunohistochemical estrogen receptor
                          analysis in primary and metastatic uveal melanoma
AUTHOR(S):                Makitie, Teemu; Tarkkanen, Ahti; Kivela, Tero
CORPORATE SOURCE:         Ophthalmic Pathology Laboratory, Department of
                          Ophthalmology, Helsinki University Central Hospital,
                          Hyks, FIN-00029, Finland
SOURCE:                   Graefe's Archive for Clinical and Experimental
                          Ophthalmology (1998), 236(6), 415-419
                          CODEN: GACODL; ISSN: 0721-832X
PUBLISHER:                Springer-Verlag
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          35    THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20  ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1994:188128  CAPLUS
DOCUMENT NUMBER:          120:188128
TITLE:                    The mouse brown (b) locus protein has dopachrome
                          tautomerase activity and is located in lysosomes in
                          transfected fibroblasts
AUTHOR(S):                Winder, Alison J.; Wittbjer, Anna; Rosengren, Evald;
                          Rorsman, Hans
CORPORATE SOURCE:         Sir William Dunn Sch. Pathol., Univ. Oxford Rd,
                          Oxford, OX1 3RE, UK
SOURCE:                   Journal of Cell Science (1993), 106(1), 153-66
                          CODEN: JNCSAI; ISSN: 0021-9533
DOCUMENT TYPE:            Journal
LANGUAGE:                 English

L20  ANSWER 3 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1992:4874  CAPLUS
DOCUMENT NUMBER:          116:4874
TITLE:                    Monoclonal antibody against a melanosomal
                          protein in melanotic and amelanotic human melanoma
                          cells
AUTHOR(S):                McEwan, Max; Parsons, Peter G.; Moss, Denis J.;
                          Burrows, Scott; Stenzel, Debbie; Bishop, Chris J.;
                          Strutton, Geoffrey M.
CORPORATE SOURCE:         Queensland Inst. Medical Res., Herston, 4006,
                          Australia
SOURCE:                   Pigment Cell Research (1989), 2(1), 1-7
                          CODEN: PCREEA; ISSN: 0893-5785
DOCUMENT TYPE:            Journal
LANGUAGE:                 English

L20  ANSWER 4 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1979:609110  CAPLUS
DOCUMENT NUMBER:          91:209110
TITLE:                    Demonstration and isolation of murine
                          melanoma-associated antigenic surface proteins
AUTHOR(S):                Gersten, Douglas M.; Marchalonis, John J.
```

CORPORATE SOURCE: Frederick Cancer Res. Cent., Natl. Cancer Inst., Frederick, MD, 21701, USA
SOURCE: Biochemical and Biophysical Research Communications (1979), 90(3), 1015-24
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

=> d abs 3

L20 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
AB BALB/c mice were immunized with tyrosinase, partially purified in 2 stages from a human melanoma cell line. A hybridoma was obtained which produced monoclonal antibody (MoAb 1C11) reactive with 8/10 melanoma cell lines and 10/10 primary cultures of human melanocytes, neval cells, and melanomas. Immunoreactivity correlated to a certain extent with tyrosinase activity but not with melanin content. No crossreactivity was obtained with neuroblastoma, medulloblastoma, fibroblasts, keratinocytes, lymphoid cells, or murine melanomas. Purification of the antigen directly from cell lysates with a MoAb 1C11 CNBr-Sepharose affinity column gave a green-brown protein of 56 kDa with no detectable tyrosinase activity. This protein was therefore different from 60 kDa active tyrosinase, identified by enzyme activity and Western blotting with a MoAb derived previously (MoAb 5C12). Unlike 5C12, 1C11 reactivity was not destroyed by pretreatment of the antigen with periodate. Immunogold labeling showed that the 1C11-reactive antigen was associated with melanosomes, and there was close correlation between 5C12 and 1C11 reactivity in resistance to trypsin and in staining various melanocytic cell populations. MoAb 1C11 may therefore recognize a polypeptide epitope in a mol. closely linked to melanin biosynthesis.

=> 6D2
6D2 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s 6D2
L21 46 6D2

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1 9970 S MELANIN
L2 61483 S MELANOMA
L3 2328 S L2 AND L1
L4 705098 S ANTIBOD?
L5 198 S L3 AND L4
L6 7 S ANTI (2W) MELANIN
L7 2 S L6 AND L2
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9 11188 S MELANIN
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11 1762 S L9 (L) L10
L12 451938 S ANTIBOD?
L13 60 S L11 AND L12
L14 190 S L9 (L) L12

```
L15          59 S L14 AND L10
L16          53 S L14 AND L13
L17          45 S L16 NOT PY>2002
L18      413661 S IN VIVO
L19           3 S L18 AND L17
L20           4 S L17 AND LABEL?
L21          46 S 6D2

=> s l21 and l10
L22           2 L21 AND L10

=> d ibib 1-2

L22  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:888105  CAPLUS
DOCUMENT NUMBER:          142:2821
TITLE:                    Dead cells in melanoma tumors
                          provide abundant antigen for targeted delivery of
                          ionizing radiation by a mAb to melanin
AUTHOR(S):                Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li;
                          Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk,
                          Jerome S.; Casadevall, Arturo
CORPORATE SOURCE:         Department of Nuclear Medicine, Albert Einstein
                          College of Medicine, Bronx, NY, 10461, USA
SOURCE:                   Proceedings of the National Academy of Sciences of the
                          United States of America (2004), 101(41), 14865-14870
                          CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:                National Academy of Sciences
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          55    THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1993:577867  CAPLUS
DOCUMENT NUMBER:          119:177867
TITLE:                    A heparan sulfate proteoglycan in developing avian
                          axonal tracts
AUTHOR(S):                Halfter, Willi
CORPORATE SOURCE:         Dep. Neurobiol., Univ. Pittsburgh, Pittsburgh, PA,
                          15261, USA
SOURCE:                   Journal of Neuroscience (1993), 13(7), 2863-73
                          CODEN: JNRSDS; ISSN: 0270-6474
DOCUMENT TYPE:            Journal
LANGUAGE:                 English


=> d kwic 2

L22  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
AB   . . . immunized with embryonic chick retina basal lamina (clones 3A 12,
     3A3, and 9E 10) and embryonic chick optic tract (clone 6D2).
     Cross-reactivity of all 4 antibodies were directed to the same antigen.
     Antibodies to heparan sulfate proteoglycan from embryonic chick muscle or
     EHS mouse tumor (perlecan) did not cross-react with the neuronal
     heparan sulfate proteoglycan, suggesting that the 2 proteoglycans are not
     related.  In Western. . .


=> s anti (2W) melanin
        393809 ANTI
             9 ANTIS
        393816 ANTI
                  (ANTI OR ANTIS)
```

```
          9775 MELANIN
          7167 MELANINS
         11188 MELANIN
                (MELANIN OR MELANINS)
L23         14 ANTI (2W) MELANIN

=> s l23 and antibod?
        451938 ANTIBOD?
L24          7 L23 AND ANTIBOD?

=> d ibib 1-7

L24  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:888105  CAPLUS
DOCUMENT NUMBER:          142:2821
TITLE:                    Dead cells in melanoma tumors provide abundant antigen
                          for targeted delivery of ionizing radiation by a mAb
                          to melanin
AUTHOR(S):                Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li;
                          Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk,
                          Jerome S.; Casadevall, Arturo
CORPORATE SOURCE:         Department of Nuclear Medicine, Albert Einstein
                          College of Medicine, Bronx, NY, 10461, USA
SOURCE:                   Proceedings of the National Academy of Sciences of the
                          United States of America (2004), 101(41), 14865-14870
                          CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:                National Academy of Sciences
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          55    THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24  ANSWER 2 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:654728  CAPLUS
DOCUMENT NUMBER:          141:186978
TITLE:                    Radiolabeled antibodies for treatment of
                          tumors
INVENTOR(S):              Dadachova, Ekaterina; Nosanchuk, Joshua D.;
                          Casadevall, Arturo
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 23 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 2004156780         A1    20040812    US 2004-775869           20040210
PRIORITY APPLN. INFO.:                       US 2003-446684P      P   20030211

L24  ANSWER 3 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:339308  CAPLUS
DOCUMENT NUMBER:          141:136788
TITLE:                    Production of melanin by Aspergillus fumigatus
AUTHOR(S):                Youngchim, Sirida; Morris-Jones, Rachael; Hay,
                          Roderick J.; Hamilton, Andrew J.
CORPORATE SOURCE:         Dermatology Department, St Johns Institute of
                          Dermatology, Guy's Hospital, Kings and St Thomas'
                          Medical Schools, London, UK
SOURCE:                   Journal of Medical Microbiology (2004), 53(3), 175-181
                          CODEN: JMMIAV; ISSN: 0022-2615
PUBLISHER:                Society for General Microbiology
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DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:639215 CAPLUS
DOCUMENT NUMBER: 137:307123
TITLE: Histoplasma capsulatum synthesizes melanin-like pigments in vitro and during mammalian infection
AUTHOR(S): Nosanchuk, Joshua D.; Gomez, Beatriz L.; Youngchim, Sirida; Diez, Soraya; Aisen, Philip; Zancope-Oliveira, Rosely M.; Restrepo, Angela; Casadevall, Arturo; Hamilton, Andrew J.
CORPORATE SOURCE: Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Infection and Immunity (2002), 70(9), 5124-5131
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:457194 CAPLUS
DOCUMENT NUMBER: 133:85156
TITLE: Human melanin concentrating hormone receptor MCH1 and cDNA and diagnostic and therapeutic uses thereof
INVENTOR(S): Salon, John A.; Laz, Thomas M.; Nagorny, Raisa; Wilson, Amy E.
PATENT ASSIGNEE(S): Synaptic Pharmaceutical Corporation, USA
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039279	A2	20000706	WO 1999-US31169	19991230
WO 2000039279	A3	20001102		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6221613	B1	20010424	US 1998-224426	19981231
CA 2358687	AA	20000706	CA 1999-2358687	19991230
AU 2000033430	A5	20000731	AU 2000-33430	19991230
AU 774398	B2	20040624		
EP 1141020	A2	20011010	EP 1999-969993	19991230
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002533116	T2	20021008	JP 2000-591172	19991230
US 6221616	B1	20010424	US 2000-478601	20000106
US 6291195	B1	20010918	US 2000-478602	20000106
US 2002111306	A1	20020815	US 2001-885478	20010620
US 6723552	B2	20040420		

US 2003082623	A1	20030501	US 2001-899732		20010705
US 2003077701	A1	20030424	US 2001-29314		20011220
US 2004038855	A1	20040226	US 2003-341751		20030114
US 2004248173	A1	20041209	US 2004-825581		20040415
PRIORITY APPLN. INFO.:			US 1998-224426	A2	19981231
			WO 1999-US31169	W	19991230
			US 2000-610635	A2	20000705
			US 2001-885478	A1	20010620
			US 2001-899732	A1	20010705

L24 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:408610 CAPLUS
DOCUMENT NUMBER: 131:180636
TITLE: Structure and function of human prepro-orexin gene
AUTHOR(S): Sakurai, Takeshi; Moriguchi, Takashi; Furuya, Keiko; Kajiwara, Noriko; Nakamura, Toshiaki; Yanagisawa, Masashi; Goto, Katsutoshi
CORPORATE SOURCE: Institute of Basic Medical Sciences, University of Tsukuba, Tsukuba, 305-8575, Japan
SOURCE: Journal of Biological Chemistry (1999), 274(25), 17771-17776
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:465553 CAPLUS
DOCUMENT NUMBER: 115:65553
TITLE: Mammalian melanin-concentrating hormones (MCHs) and methods of treatment using same
INVENTOR(S): Vaughan, Joan; Fischer, Wolfgang Hermann; Rivier, Jean Edouard; Nahon, Jean Louis Marie; Presse, Francoise Genevieve; Vale, Wylie Walker, Jr.
PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9011295	A1	19901004	WO 1990-US1492		19900320
W: CA, JP					
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE					
US 5049655	A	19910917	US 1989-326984		19890322
CA 2046900	AA	19900923	CA 1990-2046900		19900320
CA 2046900	C	20000822			
EP 464105	A1	19920108	EP 1990-905279		19900320
EP 464105	B1	19960814			
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE					
JP 04503812	T2	19920709	JP 1990-505271		19900320
JP 2944202	B2	19990830			
AT 141288	E	19960815	AT 1990-905279		19900320
US 5449766	A	19950912	US 1994-208531		19940309
US 5530095	A	19960625	US 1995-447613		19950523
PRIORITY APPLN. INFO.:			US 1989-326984	A	19890322
			WO 1990-US1492	W	19900320
			US 1991-733660	B3	19910722

US 1994-208531 A3 19940309
OTHER SOURCE(S): MARPAT 115:65553

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1 9970 S MELANIN
L2 61483 S MELANOMA
L3 2328 S L2 AND L1
L4 705098 S ANTIBOD?
L5 198 S L3 AND L4
L6 7 S ANTI (2W) MELANIN
L7 2 S L6 AND L2
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9 11188 S MELANIN
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11 1762 S L9 (L) L10
L12 451938 S ANTIBOD?
L13 60 S L11 AND L12
L14 190 S L9 (L) L12
L15 59 S L14 AND L10
L16 53 S L14 AND L13
L17 45 S L16 NOT PY>2002
L18 413661 S IN VIVO
L19 3 S L18 AND L17
L20 4 S L17 AND LABEL?
L21 46 S 6D2
L22 2 S L21 AND L10
L23 14 S ANTI (2W) MELANIN
L24 7 S L23 AND ANTIBOD?

=> s l24 and l10
L25 3 L24 AND L10

=> de ibib 1-3
DE IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d ibib 1-3

L25 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:888105 CAPLUS
DOCUMENT NUMBER: 142:2821
TITLE: Dead cells in melanoma tumors provide abundant antigen for targeted delivery of ionizing radiation by a mAb to melanin
AUTHOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li; Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk, Jerome S.; Casadevall, Arturo
CORPORATE SOURCE: Department of Nuclear Medicine, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2004), 101(41), 14865-14870
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:654728 CAPLUS
DOCUMENT NUMBER: 141:186978
TITLE: Radiolabeled antibodies for treatment of tumors
INVENTOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Casadevall, Arturo
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004156780	A1	20040812	US 2004-775869		20040210
PRIORITY APPLN. INFO.:			US 2003-446684P	P	20030211

L25 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:465553 CAPLUS
DOCUMENT NUMBER: 115:65553
TITLE: Mammalian melanin-concentrating hormones (MCHs) and methods of treatment using same
INVENTOR(S): Vaughan, Joan; Fischer, Wolfgang Hermann; Rivier, Jean Edouard; Nahon, Jean Louis Marie; Presse, Francoise Genevieve; Vale, Wylie Walker, Jr.
PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9011295	A1	19901004	WO 1990-US1492		19900320
W: CA, JP					
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE					
US 5049655	A	19910917	US 1989-326984		19890322
CA 2046900	AA	19900923	CA 1990-2046900		19900320
CA 2046900	C	20000822			
EP 464105	A1	19920108	EP 1990-905279		19900320
EP 464105	B1	19960814			
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE					
JP 04503812	T2	19920709	JP 1990-505271		19900320
JP 2944202	B2	19990830			
AT 141288	E	19960815	AT 1990-905279		19900320
US 5449766	A	19950912	US 1994-208531		19940309
US 5530095	A	19960625	US 1995-447613		19950523
PRIORITY APPLN. INFO.:			US 1989-326984	A	19890322
			WO 1990-US1492	W	19900320
			US 1991-733660	B3	19910722
			US 1994-208531	A3	19940309

OTHER SOURCE(S): MARPAT 115:65553

=> d kwic 3

L25 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
AB . . . characterized. The MCH and related peptides, formed from MCH precursors, are useful for treating skin disorders, suppressing proliferation of skin tumor (e.g. melanoma) cells in mammals, and modulating ACTH secretion. Also disclosed are the amino acid sequences and cDNA nucleotide sequences of rat. . .
ST rat melanin concg hormone; human melanin concg hormone; ACTH generation melanin concg hormone; skin neoplasm melanin cong hormone
IT Antibodies
RL: PROC (Process)
(to melanin-concentrating hormone of salmon, production of, for rat melanin-concentrating
hormone purification)
IT Globins
RL: BIOL (Biological study)
(α-subunits, conjugates, with melanin-concentrating hormone of salmon, for antibody production for rat melanin-concentrating hormone purification)
IT Proteins, specific or class
RL: BIOL (Biological study)
(A, conjugates, with Sepharose CL-4B and anti-salmon melanin-concentrating hormone antibody, for rat melanin-concentrating hormone purification)
IT 87218-84-6D, Melanin-concentrating hormone (Oncorhynchus keta), α-globin conjugates
RL: BIOL (Biological study)
(for antibody production for rat melanin-concentrating hormone purification)
IT 61970-08-9D, Sepharose CL-4B, conjugates with protein A and anti-salmon melanin-concentrating hormone antibodies
RL: BIOL (Biological study)
(in rat melanin-concentrating hormone purification)

=> file pctfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	61.54	63.65
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.25	-2.25

FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006
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FILE LAST UPDATED: 3 JAN 2006 <20060103/UP>
MOST RECENT UPDATE WEEK: 200552 <200552/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> UPDATING DELAYED DUE TO DELIVERY FORMAT CHANGES. <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOT YET AVAILABLE IN THIS FILE.
USE IPC7 FORMAT FOR SEARCHING THE IPC. WATCH THIS SPACE FOR FURTHER DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION ABOUT THE IPC REFORM <<<

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1 9970 S MELANIN
L2 61483 S MELANOMA

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L3          2328 S L2 AND L1
L4        705098 S ANTIBOD?
L5           198 S L3 AND L4
L6             7 S ANTI (2W) MELANIN
L7             2 S L6 AND L2
L8             0 S L7 AND L4

     FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9         11188 S MELANIN
L10       690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11         1762 S L9 (L) L10
L12       451938 S ANTIBOD?
L13           60 S L11 AND L12
L14          190 S L9 (L) L12
L15           59 S L14 AND L10
L16           53 S L14 AND L13
L17           45 S L16 NOT PY>2002
L18       413661 S IN VIVO
L19            3 S L18 AND L17
L20            4 S L17 AND LABEL?
L21           46 S 6D2
L22            2 S L21 AND L10
L23           14 S ANTI (2W) MELANIN
L24            7 S L23 AND ANTIBOD?
L25            3 S L24 AND L10

     FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006

=> s anti (2w) melanin
         167501 ANTI
            165 ANTIS
         167532 ANTI
                (ANTI OR ANTIS)
           2796 MELANIN
            190 MELANINS
           2854 MELANIN
                (MELANIN OR MELANINS)
L26           6 ANTI (2W) MELANIN

=> s l26 and antibod?
          84196 ANTIBOD?
L27           1 L26 AND ANTIBOD?

=> d ibib

L27    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2004048547 PCTFULL  ED 20040615  EW 200424
TITLE (ENGLISH):        INTERMEDIN AND ITS USES
TITLE (FRENCH):         INTERMEDINE ET SES UTILISATIONS
INVENTOR(S):            HSU, Sheau, Yu Teddy, 2038 Santa Cruz Avenue, Menlo
                        Park, CA 94025, US
PATENT ASSIGNEE(S):     THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR
                        UNIVERSITY, 1705 El Camino Real, Palo Alto, CA
                        94306-1106, US [US, US]
AGENT:                  SHERWOOD, Pamela J.$, BOZICEVIC, FIELD & FRANCIS LLP,
                        200 Middlefield Road, Suite 200, Menlo Park, CA 94025$,
                        US
LANGUAGE OF FILING:     English
LANGUAGE OF PUBL.:      English
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER             KIND     DATE
                        --------------------------------
                        WO 2004048547        A2 20040610
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DESIGNATED STATES
       W:              AU CA JP
       RW (EPO):       AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU
                       MC NL PT RO SE SI SK TR
APPLICATION INFO.:     WO 2003-US37968      A  20031126
PRIORITY INFO.:        US 2002-60/429,327       20021126


=> s l26 and (cancer? or tumor? or neoplas?
UNMATCHED LEFT PARENTHESIS 'AND (CANCER?'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s l26 and (cancer? or tumor? or neoplas?)
         74539 CANCER?
         62442 TUMOR?
         21534 NEOPLAS?
L28          3 L26 AND (CANCER? OR TUMOR? OR NEOPLAS?)

=> d ibib 1-3

L28    ANSWER 1 OF 3      PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2004087128 PCTFULL  ED 20041019  EW 200442
TITLE (ENGLISH):        METHYL-&Beta;-ORCINOLCARBOXYLATE FROM LICHEN
                        (EVERNIASTRUM CIRRHATUM) FOR USE FOR THE TREATMENT OF
                        FUNGAL INFECTIONS AND CANCER
TITLE (FRENCH):         METHYL-BETA-ORCINOL-CARBOXYLATE TIRE DU LICHEN
                        EVERNIASTRUM CIRRHATUM DESTINE AU TRAITEMENT
                        D'INFECTIONS FONGIQUES ET DU CANCER
INVENTOR(S):            KHANUJA, Suman, Preet, Singh, Central Institute Of
                        Medicinal And Aromatic Plants, P.O. CIMAP, Lucknow 226
                        015, Uttar Pradesh, IN;
                        TIRUPPADIRIPULIYUR, Ranganathan, Santha, Kumar, Central
                        Institute of Medicinal and Aromatic Plants, P.O. CIMAP,
                        Lucknow 226 015, Uttar Pradesh, IN;
                        GUPTA, Vivek, Kumar, Central Institute of Medicinal and
                        Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                        Pradesh, IN;
                        CHAND, Preeti, Central Institute of Medicinal and
                        Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                        Pradesh, IN;
                        GARG, Ankur, Central Institute of Medicinal and
                        Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                        Pradesh, IN;
                        SRIVASTAVA, Santosh, Kumar, Central Institute of
                        Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226
                        015, Uttar Pradesh, IN;
                        VERMA, Subash, Chandra, Central Institute of Medicinal
                        and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                        Pradesh, IN;
                        SAIKIA, Dharmendra, Central Institute of Medicinal and
                        Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                        Pradesh, IN;
                        DAROKAR, Mahendra, Pandurang, Central Institute of
                        Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226
                        015, Uttar Pradesh, IN;
                        SHASANY, Ajit, Kumar, Central Institute of Medicinal
                        and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                        Pradesh, IN;
                        PAL, Anirban, Central Institute of Medicinal and
                        Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                        Pradesh, IN
PATENT ASSIGNEE(S):     COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, Rafi
                        Marg, New Delhi 110 001, IN [IN, IN]
```

AGENT: SUBRAMANIAM, Hariharan$, Subramaniam, Nataraj & Associates, E-556 Greater Kailash II, New Delhi 110 048$, IN
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004087128	A1	20041014

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2003-IN97 A 20030331

L28 ANSWER 2 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2004048547 PCTFULL ED 20040615 EW 200424
TITLE (ENGLISH): INTERMEDIN AND ITS USES
TITLE (FRENCH): INTERMEDINE ET SES UTILISATIONS
INVENTOR(S): HSU, Sheau, Yu Teddy, 2038 Santa Cruz Avenue, Menlo Park, CA 94025, US
PATENT ASSIGNEE(S): THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, 1705 El Camino Real, Palo Alto, CA 94306-1106, US [US, US]
AGENT: SHERWOOD, Pamela J.$, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road, Suite 200, Menlo Park, CA 94025$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004048547	A2	20040610

DESIGNATED STATES
W: AU CA JP
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
APPLICATION INFO.: WO 2003-US37968 A 20031126
PRIORITY INFO.: US 2002-60/429,327 20021126

L28 ANSWER 3 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2003035167 PCTFULL ED 20030512 EW 200318
TITLE (ENGLISH): DEVICE AND METHOD FOR CONTROLLED DELIVERY OF ACTIVE SUBSTANCE INTO THE SKIN
TITLE (FRENCH): DISPOSITIF ET PROCEDE DE LIBERATION CONTROLEE D'UNE SUBSTANCE ACTIVE DANS LA PEAU
INVENTOR(S): MAVOR, Daniela, 36 Striker Street, 62006 Tel Aviv, IL [IL, IL];
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ARBEL, Giora, 5 David Hamelech Street, 44430 Kfar Saba, IL [IL, IL];
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[IL, IL];
GROSS, Yossi, Moshav Mazor 205, 73160 Moshav Mazor, IL [IL, IL]

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ARBEL, Giora, 5 David Hamelech Street, 44430 Kfar Saba, IL [IL, IL], for US only;
HAREL, Nurit, 5 Benayahu Street, 69084 Tel Aviv, IL [IL, IL], for US only;
GROSS, Yossi, Moshav Mazor 205, 73160 Moshav Mazor, IL [IL, IL], for US only

AGENT: REINHOLD COHN AND PARTNERS$, P.O.B. 4060, 61040 Tel Aviv$, IL

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2003035167	A2	20030501

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-IL849 A 20021023
PRIORITY INFO.: US 2001-60/330,526 20011024
US 2002-60/401,771 20020808

```
=> s WO 199011295/pn
L29          1 WO 199011295/PN
                 (WO9011295/PN)

=> s melanin and l29
          2796 MELANIN
           190 MELANINS
          2854 MELANIN
                 (MELANIN OR MELANINS)
L30          1 MELANIN AND L29

=> s l30 and antibod?
         84196 ANTIBOD?
L31          1 L30 AND ANTIBOD?

=> s cancer? or tumor? or neoplas?
         74539 CANCER?
         62442 TUMOR?
         21534 NEOPLAS?
L32      93014 CANCER? OR TUMOR? OR NEOPLAS?

=> s l32 and l31
```

L33 1 L32 AND L31

=> d kwic

L33 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN MELANIN-CONCENTRATING HORMONES AND METHODS OF TREATMENT USING SAME
PI WO 9011295 A1 19901004
ABEN Mammalian melanin-concentrating hormone (MCH) is isolated from rat tissue, purified and characterized. These MCH peptides are useful for treating skin disorders, for suppressing the proliferation of skin tumor cells, such as melanomas in mammals, and for modulating the secretion of ACTH. Generally, peptides are provided which have formula. . . are thought to be formed from the MCH precursors, are the peptides with the sequence H-Glu-Ile-Gly-Asp-Glu-Glu-Asn-Ser-Ala-Lys-Phe-Pro-Ile-NH2, which is cross-reactive with antibodies against alpha-MSH and CRF, and the peptides with the sequence H-Gly-XNGE-Phe-Pro-Ala-Glu-Asn-Gly-Val-Gln-Asn-Thr-Glu-Ser-Thr-Gln-Glu-OH, wherein XNGE is Pro-Ala-Val or Ser-Val-Ala, which is cross-reactive with antibodies against GRF.
ABFR . . . caracterisee. Ces peptides de MCH sont utiles pour traiter des troubles de la peau, pour supprimer la proliferation de cellules tumorales de la peau, telles que les melanomes chez les mammiferes, et pour moduler la secretion de ACTH. En general, les. . .

DETD MELANIN-CONCENTRATING HORNONES
AND METHODS OF TREATMMff USING SAME
This invention relates to hormones for concentrating melanin in mammals and to methods of treating mammals using such hormones,
BACKGROUND OF THE INVENTION
A cyclic heptadecapeptide which induces melanosome aggregation within fish. . .

et al., Nature, 305, 321-323 (1983), and it was named melanin concentrating hormone (MCH). Fish MCH has been reported to have the opposite effect, i.e., causing dispersal of melanosomes, in amphibians, Wilkes, B.. . .
. . .
mammals to lighten skin color, as by local or topical application. It is also useful to suppress the proliferation of certain skin tumor cells, such as melanomas, when suitably applied as by topical application or the like. It is also found that mammalian MCH can. . .
. . .
at position 144 of the MCH precursors would provide the NH2 group of the C-terminal amide of NEI. It has been found that antibodies against human alpha-MSH (i.e., alpha]melanocyte stimulating hormone) and human CRF (corticotropin-releasing factor) cross]react with NEI, with the anti-alpha-MSH antibodies recognizing an epitope including the N-terminus of NEI and the anti-CRF antibodies recognizing an epitope including the C-terminus of NEI, It is thought that NEI has a biological function in vivo-,
The sequences of the NGE's correspond to the

sequences of amino acids 110 - 128 of the MCH precursors (see Tables 1 and 2, below). Antibodies against human GRF (growth hormone releasing factor) cross]react with NGE, as suggested by our discovery of the close homology between the sequence Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu. . .

NEI is useful, in the process of making anti-alpha-MSH or anti]CRF monoclonal antibody]secreting hybridomas, as an immunogen for obtaining anti-alpha-MSH or anti-CRF antibody]producing splenocytes or lymphocytes and as an antigen for screening cultures of hybridomas for those which include hybridomas that make anti-MSH or anti-CRF antibodies. Similarly, NGE is useful in the process of making anti-GRF monoclonal antibody-secreting hybridomas. Monoclonal antibodies made by such hybridomas are useful for assaying for alpha]MSH, CRF or GRF by standard immunoassay methods.

Further, such a monoclonal antibody made with NEI or NGE as the immunogen, when used in a standard immunoaassay procedure in conjunction with a second monoclonal antibody, which recognizes an epitope of alpha-MSH, CRF or GRF different from the epitope recognized by the monoclonal antibody made with NEI or NGE as the immunogen, can be used to confirm that a peptide detected in an immunoassay is alpha-MSH,. . . between NEI and alpha]MSH, NEI
and CRF, or NGE and GRF. Such a confirmatory assay would be useful, for example, in assaying tumor cells, from a patient thought to be suffering from a cancer involving aberrant expression of alpha-MSH, CRF or GRF, to ascertain whether the cancer does in fact entail aberrant expression of one of those hormones or entails instead aberrant expression of NEI, NGE or some other. . .

DETAILED DESCRIPTION OF THE INVENTION
Mammalian melanin-concentrating hormone (MCH) has now been isolated from rat hypothalami by acid extraction and purified substantially by immunoaffinity chromatography using antiserum directed against salmon MCH,. . .
. . .
color of a mammal comprising administering thereto an effective amount of such a MCH, a method of suppressing the proliferation of skin tumor cells in a mammal comprising administering thereto an effective amount of such a MCH, and a method of suppressing the secretion of ACTH. . .
. . .
through nucleic acid probe hybridization analysis clones containing MCH-encoding sequences. If the library is an expression library, screening of the library with anti-MCH antibodies (alone or together with anti-NEI or anti-NGE antibodies) may also be used, alone or in conjunction with nucleic acid probe hybridization probing, to identify or confirm the presence of MCH-encoding or. . .

Throughout the purification, fractions are monitored using an RIA based upon this rabbit anti-salmon MCH antibody. Aliquots for assay are transferred into glass tubes containing BSA (10 Al of 10 mg/ml) and dried in a Savant Speed Vac.. . . is carried out using chilled reagents and with tubes partially immersed in ice

water. On day one, 100 Al of buffer with Antibody PBL #171 1/24,000 dilution (1/120,000 final dilution) is added to glass tubes containing standard or test samples or buffer only in a volume. . . to all tubes. The tubes are vortexed and returned to the cold for approximately 24 hours. On day three, tracer bound to antibody is precipitated with sheep anti]rabbit gamma globulins (100 Ali 1/40 dilution) and 0.5 ml of 10%(w/v) polyethylene glycol (SIGMA, MW = 6,000 to. . .

. . .

supernatant removed, and the reaction stopped by resuspending the beads in 20 volumes (200 mls) of 0.02 M ethanolamine-Cl, pH 8 The antibody]Protein A beads are then washed twice with 1 N HAc and equilibrated with 50 mM Na HEPES, 150 mM NaCl, pH 7*5e. . .

. . .

of the peptide for the topical application, and, in this respect, could rely upon data generated in connection with the use of MSH (melanin stimulating hormone) antagonists for this purpose.

CLMEN I. A cyclic mammalian hormone capable of concentrating mammalian melanin, which is a peptide with about 19 residues, or a physiologically acceptable salt of said mammalian hormone.

2* A mammalian hormone in accordance. . . which, if expressed, would yield a polypeptide with the amino acid sequence of a cyclic mammalian hormone, which is capable of concentrating mammalian melanin and is a peptide with about 19 residues, or, if said hormone is C]terminally amidated, said amino acid sequence with a Gly. . .

```
=> s antibod? same melanin
         84196 ANTIBOD?
        661070 SAME
           391 SAMES
        661322 SAME
                  (SAME OR SAMES)
          2796 MELANIN
           190 MELANINS
          2854 MELANIN
                  (MELANIN OR MELANINS)
L34          0 ANTIBOD? SAME MELANIN
                  (ANTIBOD?(W)SAME(W)MELANIN)

=> s antibod? (S) melanin
         84196 ANTIBOD?
          2796 MELANIN
           190 MELANINS
          2854 MELANIN
                  (MELANIN OR MELANINS)
L35        118 ANTIBOD? (S) MELANIN

=> d his

     (FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

     FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1          9970 S MELANIN
L2         61483 S MELANOMA
L3          2328 S L2 AND L1
L4        705098 S ANTIBOD?
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L5          198 S L3 AND L4
L6            7 S ANTI (2W) MELANIN
L7            2 S L6 AND L2
L8            0 S L7 AND L4

     FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9        11188 S MELANIN
L10      690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11        1762 S L9 (L) L10
L12      451938 S ANTIBOD?
L13          60 S L11 AND L12
L14         190 S L9 (L) L12
L15          59 S L14 AND L10
L16          53 S L14 AND L13
L17          45 S L16 NOT PY>2002
L18      413661 S IN VIVO
L19           3 S L18 AND L17
L20           4 S L17 AND LABEL?
L21          46 S 6D2
L22           2 S L21 AND L10
L23          14 S ANTI (2W) MELANIN
L24           7 S L23 AND ANTIBOD?
L25           3 S L24 AND L10

     FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006
L26           6 S ANTI (2W) MELANIN
L27           1 S L26 AND ANTIBOD?
L28           3 S L26 AND (CANCER? OR TUMOR? OR NEOPLAS?)
L29           1 S WO 199011295/PN
L30           1 S MELANIN AND L29
L31           1 S L30 AND ANTIBOD?
L32       93014 S CANCER? OR TUMOR? OR NEOPLAS?
L33           1 S L32 AND L31
L34           0 S ANTIBOD? SAME MELANIN
L35         118 S ANTIBOD? (S) MELANIN

=> s l32 and l35
L36         106 L32 AND L35

=> s melanin/ab
            214 MELANIN/AB
              9 MELANINS/AB
L37         217 MELANIN/AB
                  ((MELANIN OR MELANINS)/AB)

=> s melanin/ti
            100 MELANIN/TI
              6 MELANINS/TI
L38         106 MELANIN/TI
                  ((MELANIN OR MELANINS)/TI)

=> s l38 or l37
L39         239 L38 OR L37

=> s l39 and l36
L40          12 L39 AND L36

=> d ibib 1-6

L40    ANSWER 1 OF 12    PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        2004093518 PCTFULL  ED 20041110  EW 200445
TITLE (ENGLISH):         IMMUNOSTIMULATORY AGENTS IN BOTANICALS
TITLE (FRENCH):          AGENTS IMMUNOSTIMULATEURS PRESENTS DANS DES PRODUITS
                         PHYTOPHARMACEUTIQUES
```

INVENTOR(S): PASCO, David S, 706 Oakhill Drive, Oxford, MS 38655, US [US, US];
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MORAES, Rita, 307 Deer Run, Oxford, MS 38655, US [US, US]

PATENT ASSIGNEE(S): THE UNIVERSITY OF MISSISSIPPI, 125 Old Chemistry, University, MS 38677, US [US, US], for all designates States except US;
PASCO, David S, 706 Oakhill Drive, Oxford, MS 38655, US [US, US], for US only;
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KHAN, Ikhlas, A, Shelia Drive 65, Oxford, MS 38655, US [US, US], for US only;
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LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004093518	A2	20041104

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO): BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2004-US11886 A 20040416
PRIORITY INFO.: US 2003-60/463,169 20030416
US 2004-60/538,676 20040123

L40 ANSWER 2 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2002008290 PCTFULL ED 20020814
TITLE (ENGLISH): DOG MELANIN-CONCENTRATING HORMONE RECEPTOR
TITLE (FRENCH): RECEPTEUR DE L'HORMONE CONCENTRANT LA MELANINE DU CHIEN
INVENTOR(S): TAN, Carina, P.
PATENT ASSIGNEE(S): MERCK &CO., INC.;
TAN, Carina, P.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002008290	A1	20020131

DESIGNATED STATES
W: CA JP US AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

APPLICATION INFO.: WO 2001-US22458 A 20010717
PRIORITY INFO.: US 2000-60/219,669 20000721

L40 ANSWER 3 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2001098464 PCTFULL ED 20020826

TITLE (ENGLISH): CONTINUOUS ADHERENT MELANOCYTE CELL LINE
TITLE (FRENCH): LIGNEE CELLULAIRE ADHERENTE CONTINUE DE MELANOCYTE
INVENTOR(S): ALEXANDER, Jeannine;
COX, William, I.
PATENT ASSIGNEE(S): AVENTIS PASTEUR LIMITED;
ALEXANDER, Jeannine;
COX, William, I.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001098464	A2	20011227

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2001-US40540 A 20010418
PRIORITY INFO.: US 2000-60/213,613 20000622

L40 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000010507 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF MELANIN FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
TITLE (FRENCH): UTILISATION DE MELANINE POUR INHIBER L'ANGIOGENESE ET LA DEGENERESCENCE MACULAIRE
INVENTOR(S): D'AMATO, Robert, J.
PATENT ASSIGNEE(S): THE CHILDREN'S MEDICAL CENTER CORPORATION;
D'AMATO, Robert, J.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000010507	A2	20000302

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1999-US19026 A 19990820
PRIORITY INFO.: US 1998-60/097,385 19980821

L40 ANSWER 5 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1999006074 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF TEXAPHYRINS IN DETECTION OF MELANIN AND MELANIN METABOLITES OF MELANOTIC MELANOMA
TITLE (FRENCH): UTILISATION DE TEXAPHYRINES DANS LA DETECTION DE LA MELANINE ET DES METABOLITES DE LA MELANINE DU MELANOME MELANIQUE
INVENTOR(S): WOODBURN, Kathryn, W.;
YOUNG, Stuart, W.
PATENT ASSIGNEE(S): PHARMACYCLICS, INC.;
WOODBURN, Kathryn, W.;
YOUNG, Stuart, W.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9906074	A1	19990211

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-US15833 A 19980729
PRIORITY INFO.: US 1997-08/903,099 19970730

L40 ANSWER 6 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1998034602 PCTFULL ED 20020514
TITLE (ENGLISH): MEDIATION OF CYTOKINES BY MELANIN
TITLE (FRENCH): REGULATION DE LA PRODUCTION DE CYTOKINES PAR LA MELANINE
INVENTOR(S): MOHAGHEGHPOUR, Nahid
PATENT ASSIGNEE(S): BIOSOURCE TECHNOLOGIES, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9834602	A2	19980813

DESIGNATED STATES
W: AU BG CA IL JP KR MX AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1998-US2971 A 19980210
PRIORITY INFO.: US 1997-8/798,846 19970212

=> d kwic 4

L40 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN USE OF MELANIN FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
ABEN Compositions and methods of using melanin, or melanin -promoting compounds, for inhibiting angiogenesis to treat angiogenesis-dependent diseases, such as macular degeneration and cancer.
ABFR . . . de melanine permettant d'inhiber l'angiogenese afin de traiter les maladies dependantes de l'angiogenese telles que la degenerescence maculaire et le cancer.

DETD . . . ANGIOGENESIS AND MACULAR DEGENERATION

Technical Field

This application relates to an inhibitor of ancriogenesis useful for treating angiogenesis-related diseases, such as macular degeneration and angiogenesis-dependent cancers. The invention further relates to novel pharmaceutical compositions and methods for treating and curing macular degeneration, and other angiogenesis-dependent diseases.

Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, tumor metastasis and abnormal growth by endothelial cells and supports the pathological damage seen in these conditions. The

diverse
pathological states created due. . .

One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the tumors are benign and regress without intervention. In more severe cases, the tumors progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of hemangiomas, the hemangiomatoses, have a high mortality rate.

. . .
damage found in hereditary
9
diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small angiomas, tumors of blood or lymph vessels. The angiomas are found in the skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal. . .

Angiogenesis is prominent in solid tumor formation and metastasis. Several lines of direct evidence now suggest that angiogenesis is essential for the growth and persistence of solid tumors and their metastases (Folkman, 1989; Hori et al., 1991; Kim et al., 1993; Millauer et al., 1994).

To stimulate angiogenesis, tumors upregulate their production of a variety of angiogenic factors, including the fibroblast growth factors (FGF and BFGF) (Kandel et al., 1991) and vascular endothelial cell growth factor/vascular permeability factor (VEGF/VPF). However, many malignant tumors also generate inhibitors of anglogenesis, including angiostatin and thrombospondin (Chen et al., 1995; Good et al., 1990; O'Reilly et al., 1994).

. . .
et al.,
1989). Several other endogenous inhibitors of angiogenesis have been-identified, although not all are associated with the presence of a tumor.

Melanin pigments play a critical role in the development of skin
cancers such as melanoma, which involves tumor
development from transformed melanocytes. Light-skinned individuals with more pheomelanin tend to have a higher incidence of melanoma than darker skinned individuals, perhaps due. . .

. . .
melanomas. This teaches away the current invention in which increased levels of melanin are disclosed to decrease angiogenesis (blood vessel formation in tumors) and thus lead to decreased
tumor size and formation.

. . .
for treating or for repressing macular degeneration. Administration of melanin, or a melanin-promoting compound to a human or animal with prevascularized metastasized tumors

prevents the growth or expansion of those tumors.

The present invention also includes diagnostic methods and kits for detection and measurement of melanin, or a melanin -promoting compound, in biological fluids and tissues, and for localization of melanin, or a melanin-promoting compound, in tissues. The diagnostic method and kit can be in any configuration well known to those of ordinary skill in the art. The present invention also includes antibodies specific for the melanin, or a melanin-promoting compound, and antibodies that inhibit the binding of antibodies specific for the melanin, or a melanin-promoting compound.

The antibodies specific for melanin, or a melanin-promoting compound, can be used in diagnostic kits to detect the presence and quantity of melanin, or a melanin-promoting compound, which is diagnostic or prognostic for the occurrence or recurrence of cancer or other disease mediated by angiogenesis. Antibodies specific for melanin, or a melanin-promoting compound, may also be administered to a human or animal to passively immunize the human or animal against melanin, or a melanin-promoting compound, thereby reducing angiogenic inhibition.

The present invention also relates to methods of using the melanin, or a melanin-promoting compound, fragments, and antibodies that bind specifically to the inhibitor and its fragments, to diagnose endothelial cell-related diseases and disorders.

. . .

that are mediated by angiogenesis including, but not limited to macular degeneration, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, hemangioma, solid tumors , leukernia, metastasis, telanglectasia psoriasis scleroderma, pyogenic granuloma,

myocardial anglogenesis, plaque neovascularization, corornay collaterals, cerebral collaterals, arteriovenous malformations, ischernic limb angiogenesis, arthritis, diabetic. . .

It is another object of the present invention to provide a composition for treating or repressing the growth of a cancer.

It is an object of present invention to provide a method for detecting and quantifying the presence of an antibody specific for an melanin, or a melanin-promoting compound, in a body fluid.

Still another object of the present invention is to provide a composition consisting of antibodies to melanin, or a melanin-promoting

compound, that are selective for specific regions of the melanin , or a melanin-promoting compound, molecule.

It is another object of the present invention to provide a method for the detection or prognosis of cancer.

Still another object of the present invention is to provide a composition comprising melanin, or a melanin-promoting compound, linked to a cytotoxic agent for treating or repressing the growth of a cancer.

. . . inhibiting angiogenesis are melanin and melanin-promoting compounds. The inhibitor compounds of the invention are useful for treating angiogenesis-related diseases, particularly macular degeneration, and angiogenesis-dependent cancers and tumors. The unexpected and surprising ability of melanin to treat and cure anglogenesis-dependent diseases answers a long felt and unfulfilled need in the. . .

. . . inhibiting activity include the chick CAM assay, the mouse corneal assay, and the effect of administering isolated or synthesized proteins on implanted tumors. The chick CAM assay is described by O'Reilly, et al. in Angiogenic Regulation of Metastatic Growth Cell, vol. 79 (2), October 21,. . .

Cancer means angiogenesis-dependent cancers and tumors, i.e. tumors that require for their growth (expansion in volume and/or mass) an increase in the number and density of the blood vessels supplying. . .

Regression refers to the reduction of tumor mass and size.

. . . melanin, or a melanin-promoting compound, in body fluids and tissues for the purpose of diagnosis or prognosis of angiogenesis-mediated diseases such as cancer.

. . . tissues. The present invention also includes methods of treating or preventing angiogenic diseases and processes including, but not limited to, macular degeneration and tumors by stimulating the production of melanin, and/or by administering substantially purified melanin, or a melanin-associated compound, or a fusion protein containing the. . .

Passive antibody therapy using antibodies that specifically bind melanin can be employed to modulate endothelial-dependent processes such as reproduction, development, and wound healing and tissue repair.

Antibodies specific for melanin, or a melanin-promoting compound, are made according to techniques and protocols well-known in the art. The - 13 - antibodies may be either polyclonal or monoclonal. The antibodies are utilized in well-know immunoassay formats, such as competitive and non-competitive immunoassays, including ELISA, sandwich immunoassays and

radioimmunoassays (RlAs), to determine the. . .
. . .
limited to,
ocular angiogenic diseases, for example, diabetic retinopathy,
retinopathy of
prematurity, macular degeneration, corneal graft rejection, neovascular
glaucoma, retrolental fibroplasia, rubeosis; angiogenesis-dependent
cancer,
including, for example, solid tumors, blood born
tumors such as leukemias,
and tumor metastases; benign tumors, for example
hemangiomas, acoustic
neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid
arthritis; psoriasis; Osler-Webber Syndrome; myocardial angiogenesis;
plaque neovascularization; telangiectasia; hemophiliac joints;
angiofibroma;
and. . .
. . .
cardiac muscle
especially following transplantation of a heart or heart tissue and
after
bypass surgery, promotion of vascularization of solid and relatively
avascular tumors for enhanced cytotoxin delivery, and
enhancement of
blood flow to the nervous system, including but not limited to the
cerebral
cortex and. . .
. . .
destruction of cells that bind melanin. These cells may
be found in many locations, including but not limited to,
micrometastases
and primary tumors. Peptides linked to cytotoxic agents are
infused in a
manner designed to maximize delivery to the desired location. For
example,
ricin-linked high. . . antagonists may be co-applied
with stimulators of anglogenesis to increase vascularization of tissue.
This
therapeutic regimen provides an effective means of destroying metastatic
cancer.
. . .
a melanin-
promoting compound, may be used in combination with other compositions
and procedures for the treatment of diseases. For example, a
tumor may be
treated conventionally with surgery, radiation or chemotherapy combined
with melanin, and then another anti-angiogenic compound may be
subsequently administered to the patient to extend the dormancy of
micrometastases and to stabilize any residual primary tumor.
. . .
the compound, the
polymers being implanted in the vicinity of where drug delivery is
desired,
for example, at the site of a tumor or implanted so that the
endostatin is
slowly released systemically. Osmotic minipumps may also be used to
provide controlled delivery of high. . . through cannulae to the site
of interest, such as
directly into a metastatic growth or into the vascular supply to that
tumor.

Kits for measurement of melanin, or a melanin
-promoting
compound, are also contemplated as part of the present invention.

Antisera
that possess the highest titer and specificity and can detect the. . .
and non-competitive assays,
radioimmunoassay, bioluminescence and chemiluminescence assays,
fluorometric assays, sandwich assays, immunoradiometric assays, dot
blots,
enzyme linked assays including ELISA, microtiter plates,
antibody coated
- 18 -
strips or dipsticks for rapid monitoring of urine or blood, and
immunocytochernistry. For each kit the range, sensitivity, precision,
reliability,. . .
. . .
in the pigmented layer of the eye,
or choroid, compared to white patients. Additionally, black patients
have a
reduced incidence of vascular tumors in the skin such as
childhood
hemangiomas. However, there are other inherent racial differences
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white and black individuals besides pigmentation, and. . .
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strategy to
discover circulating angiogenesis inhibitors generated by human
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Cancer Res. 55, 4230
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angiogenesis suppresses tumor growth in vivo. Nature 362, 841

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recombinant human platelet factor-4 and related peptides. Science 247,
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Menon, et al. (1983), 443 Cancer Research 3165.
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B., and
McFerran, N. V. (1995). Murine epidermal growth factor (EGF) fragment
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O'Reilly, M. S., Holingren, L., Chen, C. C., and Folkman, J. (1996).

Angiostatin induces and sustains dormancy of human primary
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Rehn, M., and Pihlajaniemi, T. (1994). al(XV111), a collagen chain with
frequent interruptions in the collagenous sequence,. . .

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Inhibition
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CDPGYIGSR-NH2. Cancer Res. 51, 903
Salorninski and Paus, (1994) 103 J. Invest. Derm. 742.

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Nad. Cancer Inst. 87, 581
Weiter, et al., (1985) 99 Am. J. Ophthal 185.

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L40 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000010507 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF MELANIN FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
TITLE (FRENCH): UTILISATION DE MELANINE POUR INHIBER L'ANGIOGENESE ET LA DEGENERESCENCE MACULAIRE
INVENTOR(S): D'AMATO, Robert, J.
PATENT ASSIGNEE(S): THE CHILDREN'S MEDICAL CENTER CORPORATION; D'AMATO, Robert, J.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000010507	A2	20000302

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1999-US19026 A 19990820
PRIORITY INFO.: US 1998-60/097,385 19980821
TIEN USE OF MELANIN FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
ABEN Compositions and methods of using melanin, or melanin -promoting compounds, for inhibiting angiogenesis to treat angiogenesis-dependent diseases, such as macular degeneration and cancer.
ABFR . . . de melanine permettant d'inhiber l'angiogenese afin de traiter les maladies dependantes de l'angiogenese telles que la degenerescence maculaire et le cancer.

DETD . . . ANGIOGENESIS AND MACULAR DEGENERATION
Technical Field
This application relates to an inhibitor of ancriogenesis useful for treating angiogenesis-related diseases, such as macular degeneration and angiogenesis-dependent cancers. The invention further relates to novel pharmaceutical compositions and methods for treating and curing macular degeneration, and other angiogenesis-dependent diseases.

Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, tumor metastasis and abnormal growth by endothelial cells and supports the pathological damage seen in these conditions. The diverse pathological states created due. . .

One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the tumors are benign and regress without intervention. In more severe cases, the tumors progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of

hemangiomas, the hemangiomatoses, have a high mortality rate.
. . .
damage found in hereditary
9
diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small
angiomas, tumors of blood or lymph vessels. The angiomas are found in the
skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal. . .

Angiogenesis is prominent in solid tumor formation and metastasis. Several lines of direct evidence now suggest that angiogenesis is
essential for the growth and persistence of solid tumors and their metastases
(Folkman, 1989; Hori et al., 1991; Kim et al., 1993; Millauer et al., 1994).

To stimulate angiogenesis, tumors upregulate their production of a variety of
angiogenic factors, including the fibroblast growth factors (FGF and BFGF)
(Kandel et al., 1991) and vascular endothelial cell growth factor/vascular
permeability factor (VEGF/VPF). However, many malignant tumors also
generate inhibitors of anglogenesis, including angiostatin and thrombospondin (Chen et al., 1995; Good et al., 1990; O'Reilly et al., 1994).
. . .
et al.,
1989). Several other endogenous inhibitors of angiogenesis have been-identified, although not all are associated with the presence of a tumor.

Melanin pigments play a critical role in the development of skin
cancers such as melanoma, which involves tumor
development from
transformed melanocytes. Light-skinned individuals with more pheomelanin tend to have a higher incidence of melanoma than darker skinned individuals, perhaps due. . .
. . .
melanomas. This teaches away the current
invention in which increased levels of melanin are disclosed to decrease angiogenesis (blood vessel formation in tumors) and thus lead to decreased
tumor size and formation.
. . .
for treating or for repressing macular
degeneration. Administration of melanin, or a melanin-promoting compound to a human or animal with prevascularized metastasized tumors
prevents the growth or expansion of those tumors.

The present invention also includes diagnostic methods and kits for detection and measurement of melanin, or a melanin -promoting
compound, in biological fluids and tissues, and for localization of melanin,
or a melanin-promoting compound, in tissues. The diagnostic method and
kit can be in any configuration well known to those of ordinary skill in

the
art. The present invention also includes antibodies specific
for the melanin,
or a melanin-promoting compound, and antibodies that
inhibit the binding of
antibodies specific for the melanin, or a
melanin-promoting compound.

The antibodies specific for melanin, or a
melanin-promoting compound, can
be used in diagnostic kits to detect the presence and quantity of
melanin, or a
melanin-promoting compound, which is diagnostic or prognostic
for the
occurrence or recurrence of cancer or other disease mediated
by
angiogenesis. Antibodies specific for melanin, or a
melanin-promoting
compound, may also be administered to a human or animal to passively
immunize the human or animal against melanin, or a
melanin-promoting
compound, thereby reducing angiogenic inhibition.

The present invention also relates to methods of using the
melanin, or a melanin-promoting compound, fragments,
and antibodies that
bind specifically to the inhibitor and its fragments, to diagnose
endothelial
cell-related diseases and disorders.
. . .
that are
mediated by angiogenesis including, but not limited to macular
degeneration, corneal diseases, rubeosis, neovascular glaucoma, diabetic
retinopathy, retrolental fibroplasia, hemangioma, solid tumors
, leukernia,
metastasis, telanglectasia psoriasis scleroderma, pyogenic granuloma,
- 10 -
myocardial anglogenesis, plaque neovascularization, corornay
collaterals,
cerebral collaterals, arteriovenous malformations, ischernic limb
angiogenesis, arthritis, diabetic. . .

It is another object of the present invention to provide a
composition for treating or repressing the growth of a cancer.

It is an object of present invention to provide a method for
detecting and quantifying the presence of an antibody specific
for an
melanin, or a melanin-promoting compound, in a body
fluid.

Still another object of the present invention is to provide a
composition consisting of antibodies to melanin, or
a melanin-promoting
compound, that are selective for specific regions of the melanin
, or a
melanin-promoting compound, molecule.

It is another object of the present invention to provide a method
for the detection or prognosis of cancer.

Still another object of the present invention is to provide a
composition comprising melanin, or a melanin-promoting compound, linked
to a cytotoxic agent for treating or repressing the growth of a

cancer.

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inhibiting
angiogenesis are melanin and melanin-promoting compounds. The inhibitor compounds of the invention are useful for treating angiogenesis-related diseases, particularly macular degeneration, and angiogenesis-dependent cancers and tumors. The unexpected and surprising
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Cancer means angiogenesis-dependent cancers and
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Regression refers to the reduction of tumor mass and size.

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melanin, or
a melanin-promoting compound, in body fluids and tissues for the purpose of diagnosis or prognosis of angiogenesis-mediated diseases such as cancer.

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tissues. The
present invention also includes methods of treating or preventing
angiogenic
diseases and processes including, but not limited to, macular
degeneration
and tumors by stimulating the production of melanin, and/or by administering substantially purified melanin, or a melanin-associated compound, or a fusion protein containing the. . .

Passive antibody therapy using antibodies that
specifically bind
melanin can be employed to modulate endothelial-dependent
processes such
as reproduction, development, and wound healing and tissue repair.

Antibodies specific for melanin, or a
melanin-promoting compound, are
made according to techniques and protocols well-known in the art. The
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antibodies may be either polyclonal or monoclonal. The
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utilized in well-know immunoassay formats, such as competitive and non-competitive immunoassays, including ELISA, sandwich immunoassays and radioimmunoassays (RlAs), to determine the. . .

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limited to,
ocular angiogenic diseases, for example, diabetic retinopathy,
retinopathy of
prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis; angiogenesis-dependent
cancer,
including, for example, solid tumors, blood born
tumors such as leukemias,

and tumor metastases; benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid arthritis; psoriasis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; and. . .

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cardiac muscle especially following transplantation of a heart or heart tissue and after bypass surgery, promotion of vascularization of solid and relatively avascular tumors for enhanced cytotoxin delivery, and enhancement of blood flow to the nervous system, including but not limited to the cerebral cortex and. . .

. . .

destruction of cells that bind melanin. These cells may be found in many locations, including but not limited to, micrometastases and primary tumors. Peptides linked to cytotoxic agents are infused in a manner designed to maximize delivery to the desired location. For example, ricin-linked high. . . antagonists may be co-applied with stimulators of anglogenesis to increase vascularization of tissue. This therapeutic regimen provides an effective means of destroying metastatic cancer.

. . .

a melanin-promoting compound, may be used in combination with other compositions and procedures for the treatment of diseases. For example, a tumor may be treated conventionally with surgery, radiation or chemotherapy combined with melanin, and then another anti-angiogenic compound may be subsequently administered to the patient to extend the dormancy of micrometastases and to stabilize any residual primary tumor.

. . .

the compound, the polymers being implanted in the vicinity of where drug delivery is desired, for example, at the site of a tumor or implanted so that the endostatin is slowly released systemically. Osmotic minipumps may also be used to provide controlled delivery of high. . . through cannulae to the site of interest, such as directly into a metastatic growth or into the vascular supply to that tumor.

Kits for measurement of melanin, or a melanin-promoting compound, are also contemplated as part of the present invention. Antisera that possess the highest titer and specificity and can detect the. . . and non-competitive assays, radioimmunoassay, bioluminescence and chemiluminescence assays, fluorometric assays, sandwich assays, immunoradiometric assays, dot blots, enzyme linked assays including ELISA, microtiter plates, antibody coated

strips or dipsticks for rapid monitoring of urine or blood, and

immunocytochernistry. For each kit the range, sensitivity, precision, reliability,. . .
. . .
in the pigmented layer of the eye,
or choroid, compared to white patients. Additionally, black patients have a
reduced incidence of vascular tumors in the skin such as childhood
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Menon, et al. (1983), 443 Cancer Research 3165.
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B., and
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Nad. Cancer Inst. 87, 581
Weiter, et al., (1985) 99 Am. J. Ophthal 185.

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L40 ANSWER 7 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997000892 PCTFULL ED 20020514
TITLE (ENGLISH): DEPIGMENTING ACTIVITY OF AGOUTI SIGNAL PROTEIN AND PEPTIDES THEREOF
TITLE (FRENCH): ACTIVITE DE DEPIGMENTATION DE LA PROTEINE-SIGNAL D'AGOUTI ET SES PEPTIDES
INVENTOR(S): HEARING, Vincent, J., Jr.

PATENT ASSIGNEE(S): THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY DEPARTMENT OF HEALTH AND HUMAN SERVICES;
HEARING, Vincent, J., Jr.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9700892	A2	19970109

DESIGNATED STATES
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1996-US10695 A 19960621
PRIORITY INFO.: US 1995-60/000,436 19950623

L40 ANSWER 8 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1995009629 PCTFULL ED 20020514
TITLE (ENGLISH): SYNTHETIC MELANIN
TITLE (FRENCH): MELANINE SYNTHETIQUE
INVENTOR(S): PAWELEK, John, M.
PATENT ASSIGNEE(S): YALE UNIVERSITY
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9509629	A1	19950413

DESIGNATED STATES
W: AM AU BB BG BR BY CA CN CZ EE FI GE HU JP KE KG KR KZ LK LR LT LV MD MG MN MW NO NZ PL RO RU SD SI SK TJ TT UA UZ VN KE MW SD SZ AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1994-US10835 A 19940926
PRIORITY INFO.: US 1993-131,270 19931001

L40 ANSWER 9 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1992018166 PCTFULL ED 20020513
TITLE (ENGLISH): MELANIN-BASED AGENTS FOR IMAGE ENHANCEMENT
TITLE (FRENCH): AGENTS A BASE DE MELANINE UTILISES POUR LE REHAUSSEMENT DES IMAGES
INVENTOR(S): WILLIAMS, Robert, F.
PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM;
WILLIAMS, Robert, F.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9218166	A1	19921029

DESIGNATED STATES
W: AT AU BB BE BF BG BJ BR CA CF CG CH CI CM CS DE DK ES FI FR GA GB GN GR HU IT JP KP KR LK LU MC MG ML MN MR MW NL NO PL RO RU SD SE SN TD TG US
APPLICATION INFO.: WO 1992-US3177 A 19920415
PRIORITY INFO.: US 1991-685,937 19910415

L40 ANSWER 10 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1992007580 PCTFULL ED 20020513

TITLE (ENGLISH): THERAPEUTIC USES OF MELANIN
TITLE (FRENCH): UTILISATIONS THERAPEUTIQUES DE LA MELANINE
INVENTOR(S): BERLINER, David, L.;
ERWIN, Robert, L.;
McGEE, David, R.
PATENT ASSIGNEE(S): BIOSOURCE GENETICS CORPORATION
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9207580	A1	19920514

DESIGNATED STATES
W: AT AU BE CA CH DE DK ES FI FR GB GR IT JP LU NL NO SE
APPLICATION INFO.: WO 1991-US8213 A 19911105
PRIORITY INFO.: US 1990-609,311 19901105

L40 ANSWER 11 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1990012869 PCTFULL ED 20020513
TITLE (ENGLISH): NON-MELANOCYTIC, EUCARYOTIC CELL CONSTITUTIVELY EXPRESSING BIOLOGICALLY ACTIVE HUMAN TYROSINASE AND USE THEREOF
TITLE (FRENCH): CELLULE EUCARYOTE NON MELANOCYTIQUE EXPRIMANT DE MANIERE CONSTITUTIVE LA TYROSINASE HUMAINE BIOLOGIQUEMENT ACTIVE, ET SON UTILISATION
INVENTOR(S): BOUCHARD, Brigitte;
HOUGTON, Alan, N.
PATENT ASSIGNEE(S): SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9012869	A1	19901101

DESIGNATED STATES
W: AT BE CA CH DE DK ES FR GB IT JP LU NL SE
APPLICATION INFO.: WO 1990-US2288 A 19900426
PRIORITY INFO.: US 1989-343,960 19890426

L40 ANSWER 12 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1990011295 PCTFULL ED 20020513
TITLE (ENGLISH): MELANIN-CONCENTRATING HORMONES AND METHODS OF TREATMENT USING SAME
TITLE (FRENCH): HORMONES CONCENTRANT LA MELANINE ET PROCEDES DE TRAITEMENT UTILISANT DE TELLES HORMONES
INVENTOR(S): VAUGHAN, Joan;
FISCHER, Wolfgang, Hermann;
RIVIER, Jean, Edouard;
NAHON, Jean-Louis, Marie;
PRESSE, Francoise, Genevieve;
VALE, Wylie, Walker, Jr.
PATENT ASSIGNEE(S): THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9011295	A1	19901004

DESIGNATED STATES
W: AT BE CA CH DE DK ES FR GB IT JP LU NL SE
APPLICATION INFO.: WO 1990-US1492 A 19900320
PRIORITY INFO.: US 1989-326,984 19890322

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L40 ANSWER 8 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN SYNTHETIC MELANIN
ABEN A melanin that is soluble in an aqueous solution at a pH between 5 and 9 at a temperature of 0 to 100 °C. Advantageously, the melanin is capable of being filtered through at least a 0.45 micron size filter, and has a molecular weight of greater than 10,000 kilodaltons. The melanin is useful for providing a naturally-appearing tan to mammalian skin and hair. Such melanin can be produced by combining dopachrome and an appropriate enzyme, or by incubating 5,6-dihydroxyindole-2-carboxylic acid alone or with 5,6-dihydroxyindole, or with 3-amino-tyrosine. The melanin is also useful for providing a sun-screen to mammalian skin and hair, to treat post-inflammatory hypo- and hyperpigmentation, to tint. . . as a coloring agent in foodstuffs such as coffee, tea, soda, whisky and liquors. Also included are self-tanning compositions containing melanin and DHA.

DETD . . . which absorb ultraviolet radiation and, thus, provide protection from its harmful effects, such as premature skin aging and the occurrence of skin cancers.

tyrosinase: Ann Korner and John Pawelek, Mammalian Tyrosinase Catalyzes Three Reactions in the Biosynthesis of 5 Melanin. Science, 217:1163-1165, 1982; dopachrome tautomerase: John Pawelek, After Dopachrome?, Pigment Cell Research, 4:53-62, 1991, glycoprotein 75: Timothy M. Thomson, M. Jules Mattes, Linda Roux, Lloyd Old and Kenneth 0, Lloyd, io Pigmentation-associated Glycoprotein of Human Melanomas and Melanocytes: Definition with a Mouse Monoclonal Antibody, J, Invest. Derm,, 85:169-174, 1985; MSH receptor: Seth J. Orlow, Sara Hotchkiss, and John M. Pawelek, Internal Binding Sites for MSH: Analyses in Wild Type and Variant Cloudman Melanoma Cells,, J, Cellular Physiology,, 142:129 136, 1990, The melanins according to the present invention can be admixed with a physiologically acceptable carrier to form a composition, which has the uses previously. . .

=> s wo2000010507/pn
L41 1 WO2000010507/PN
(WO2000010507/PN)

=> s l41 and label?
131550 LABEL?
L42 1 L41 AND LABEL?

=> d kwic

L42 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN
PI WO 2000010507 A2 20000302

DETD The present invention also includes melanin, or a melanin-promoting compound, that can be labeled isotopically or with other molecules or proteins for use in the detection and visualization of melanin,

or a melanin-promoting compound, sites with. . .
. . .
Sci. USA 76,
5217
Gavrieli, Y., Sherman, Y., and Ben-Sasson, S. A. (1992). Identification
of
programmed cell death in situ via specific labeling of nuclear
DNA
fragmentation. J. Cell Biol.. 119, 493
Good, D. J., Polverini, P. J., Rastinejad, F., Le Beau, M. M.,. . .

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	38.59	102.24

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NEWS	7	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS	8	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS	9	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS	10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC

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 NEWS 11  JAN 17  Pre-1988 INPI data added to MARPAT
 NEWS 12  JAN 17  IPC 8 in the WPI family of databases including WPIFV

 NEWS EXPRESS  JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
               V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
               http://download.cas.org/express/v8.0-Discover/

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FILE LAST UPDATED:         3 JAN 2006      <20060103/UP>
MOST RECENT UPDATE WEEK:       200552        <200552/EW>
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=> s wo9834602/pn
L1            1 WO9834602/PN

=> s antibod? and l1
         84196 ANTIBOD?
L2            1 ANTIBOD? AND L1

=> s l2 and melanin
           2796 MELANIN
            190 MELANINS
           2854 MELANIN
                  (MELANIN OR MELANINS)
L3            1 L2 AND MELANIN

=> d l3
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L3     ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN
AN     1998034602 PCTFULL  ED 20020514
TIEN   MEDIATION OF CYTOKINES BY MELANIN
TIFR   REGULATION DE LA PRODUCTION DE CYTOKINES PAR LA MELANINE
IN     MOHAGHEGHPOUR, Nahid
PA     BIOSOURCE TECHNOLOGIES, INC.
LA     English
DT     Patent
PI     WO 9834602           A2 19980813
DS     W:            AU BG CA IL JP KR MX AT BE CH DE DK ES FI FR GB GR IE IT
                     LU MC NL PT SE
AI     WO 1998-US2971       A  19980210
PRAI   US 1997-8/798,846       19970212
ICM    A61K031-195
ICS    A61K031:40; A61K031:785


=> d ibib kwic

L3     ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       1998034602 PCTFULL  ED 20020514
TITLE (ENGLISH):        MEDIATION OF CYTOKINES BY MELANIN
TITLE (FRENCH):         REGULATION DE LA PRODUCTION DE CYTOKINES PAR LA
                        MELANINE
INVENTOR(S):            MOHAGHEGHPOUR, Nahid
PATENT ASSIGNEE(S):     BIOSOURCE TECHNOLOGIES, INC.
LANGUAGE OF PUBL.:      English
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER              KIND     DATE
                        ---------------------------------
                          WO 9834602           A2 19980813
DESIGNATED STATES
       W:               AU BG CA IL JP KR MX AT BE CH DE DK ES FI FR GB GR IE
                        IT LU MC NL PT SE
APPLICATION INFO.:      WO 1998-US2971       A  19980210
PRIORITY INFO.:         US 1997-8/798,846       19970212
TIEN   MEDIATION OF CYTOKINES BY MELANIN
PI     WO 9834602           A2 19980813
ABEN   Methods and compositions are provided that teach the use of purified
       melanin compositions to
       treat, prevent, or ameliorate diseases that are associated with excess
       cytokine production. In
       particular, methods and compositions are.  .  .

DETD   MEDIATION OF CYTOKINES BY MELANIN
       1 FIELD OF THE INVENTION
       Methods and compositions are described for the use of purified
         melanin to treat disease in animals and man. The disclosed
       melanin
       compositions are particularly useful for regulating cytokine production
       by
       mammalian and human cells both in vitro and in vivo.
 .  .  .
       syndrome a significant
       .2 -
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       medical problem. Taken together, these results provide a mechanistic
       basis
       for considering the use of melanin, an agent that interferes
       with the
       synthesis/release of IL-1, IL-6 and TNF-cc, for managing wasting in
       patients.
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AIDS-KS derived cells produce other cytokines including IL-1 (Marx, Science 248:442-443, 1990) Addition of anti-IL-1 antibody to KS cell lines
also resulted in decreased cellular proliferation. The increased levels of
serum IL-6 and polyclonal B cell activation may. . .

A wide variety agents have been used to combat inflammation and life-threatening aspects of cytokines. Anti-TNF-a antibody, the TNF-(x
receptor, anti-IL-6,, and IL-1 receptor antagonist (IL-lRa) therapy were shown
to reduce death after acute systemic toxicity (e.g., septic shock). .
.
. . .
agent, or the site of infection (Bagby et al.,
J. Infect. Dis. l.U:83-88, 1991). Moreover, in a number of studies, anti-
cytokine antibodies only partially protected the animals
(Feingold et al., J.

Rheumatol. 20:259-262) monoclonal antibody, as well as soluble TNF-(x
receptors (Moreland et al., Arthritis Rheum. 37:S295, 1994), or soluble IL-1
receptor (Drevlow et al., Arthritis Rheum. 37:S339, 1994) is effective in the
treatment of rheumatoid arthritis. However, use of soluble cytokine receptors or antibodies to a single factor is constrained by the presence of
multiple cytokines that participate in the manifestation of inflammatory conditions. Moreover, the large-scale treatment with anticytokine antibody
may lead to production of anti-idiotypic antibodies.

Melanin,, inter alia, is a free radical scavenger that acts as a bacterial
virulence factor by protecting the organism from some host. . .

Additional studies have shown that melanin expression by bacteria may be
a virulence factor that helps bacterial pathogens avoid the afferent phase of
25 T cell-mediated immune responses. . .

3.0, SUMMARY OF THE INVENTIQN
The present invention is directed to the use of melanin as a
30 therapeutic agent in animals, including humans. The preferred method of
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treatment comprises the administration of purified melanin, or biosynthetic melanin, to an animal in an amount sufficient to alleviate or
prevent an adverse symptom of disease or illness. Accordingly, an object of
the invention is a method of using purified melanin to treat or prevent
illness in a patient which comprises administering melanin to the patient
in an amount sufficient to provide a therapeutic benefit to the patient.

In a preferred embodiment of the present invention, the purified

melanin provides a therapeutic benefit by being administered in an amount sufficient to modulate the immune response of the patient. In a particularly preferred embodiment, the purified melanin is administered in an amount sufficient to be associated with a decrease in host cytokine production, and in particular TNF-a, IL-1 and. . . decrease in cytokine production may be either a cause or effect of the beneficial clinical indications associated with the administration of purified melanins.

The purified melanins used in the presently described invention may also be administered in combination with a wide variety of pharmaceutically useful carriers or excipients. Accordingly, an additional embodiment of the present invention is the use of pharmaceutical compositions comprising purified melanin to reduce TNF-CC production or otherwise provide a therapeutic benefit to a patient.

An additional embodiment of the present invention is the use of highly purified melanins that have a substantially homogeneous structure, and are substantially free of incorporated contaminating amino acids or derivatives thereof.

The presently described therapeutic use of purified melanin is particularly deemed to be useful for the treatment of cachexia, sepsis, acute respiratory distress syndrome, cerebral malaria, rheumatoid arthritis, epithelial ulcers of. . .
. . .
that graft rejection is often associated with an inflammatory response, an additional embodiment of the present invention is the use of purified melanin, or purified synthetic melanin, to reduce or prevent the rejection of transplanted organs and grafts. Similarly, the purified melanins are also deemed to be useful in the treatment and prevention of graft-versus-host disease.
. . .
an additional embodiment of the present
10 invention is a method of modulating cytokine production by an animal cell by administering purified melanin to said cell in an amount sufficient to modulate cytokine production by said cell. In a preferred embodiment, the purified melanin will have been tested in vitro to verify that compositions comprising the purified melanin have the property of being capable of
15 modulating cytokine expression by mammalian or other animal cells.

4,0. DESCRIPTION OF JUE FIGURES

Figure 1 shows that melanin inhibits LPS-induced TNF-a
20 production. Open circles depict TNF-a production/release by monocytes (1X106 cells/ml) that were incubated for 40 min at 37'C with various concentrations of melanin AHM 8 before stimulation with 1 ng/ml LPS.

The TNF-(x concentration was also determined for supernatants collected

from monocytes stimulated with LPS in the absence of melanin (3,230
pg/ 106 cells/ml), and from supernatants collected from monocytes maintained in medium alone (36 pg/ 106 cells/ml).

Closed circles depict the effect of melanin on the constitutive
30 synthesis of protein by melanin-treated cells. Monocytes (1x10' per 0.2 ml
leucine-free medium supplemented with 10% dialyzed human AB serum)
w 9 -
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seeded in 96-well plates were incubated for 5 hr at 37'C with the indicated
concentrations of melanin AHM 8. Control cells were maintained in
medium alone for the duration of culture. At 4 hours prior to harvest, cells
were. . .

Figures 2(A-D) show that melanin significantly inhibits production of
TNF-a (Fig. 2A), IL-12 (Fig. 2B), and IL-6 (Fig. 2C), but not GM-CSF (Fig. 2D),
by human peripheral blood monocytes. Monocytes were pretreated with
the indicated concentrations of melanin AHM 8 (O]tg/ml, open bar; 50
]tg/ml, slashed bar; 100 gg/ml, solid bar) before stimulation with 1 ng/ml
LPS. Controls included (1) melanin-nontreated cells stimulated with LPS,
(2) melanin-treated, LPS-nonstimulated monocytes,, and (3) monocytes
1%5 incubated in complete medium in the absence of additives.
. . .
mean (±SEM) cytokine contents in the supernatant
collected from 106 LPS-nonstimulated monocytes incubated in the presence
of 0, 50, or 100]tg/ml melanin were, respectively, <108
±5 pg/ml, for TNF-(x;
<75 ±53 pg/ml for IL-19; <598 +238 pg/ml for IL-6; and <168
±124 pg/ml. . .

Figures 3(A & B) show duplicate experiments which indicate that the
observed reversal of melanin-mediated suppression of TNF-a production is
time-dependent. Human peripheral blood monocytes were incubated at
371C with 100 gg/ml melanin AHM 8. After a 1 hour incubation, cells were
washed to remove free melanin, suspended in fresh medium, and
stimulated with 1 ng/ml LPS at the indicated time points. The
concentration of TNF-a in culture supernatants. . .

Figure 4 shows that melanin treatment suppresses TNF-(x production
even when applied after LPS stimulation. Monocytes were stimulated with
1 ng/ml LPS either 1 hour after (open box), simultaneously with (slashed
box), or 1 hour before (solid black box) the addition of the indicated amount
of melanin (50 or 100 gg, respectively).

Control monocytes were incubated without LPS in either the absence
10 or presence of melanin (not shown). Twenty-four hours after stimulation
with LPS, the levels of TNF-cc in the culture supernatants were measured

by
ELISA. At both concentrations,. the amount TNF-(x inhibition observed was
greatest when the cells were pretreated with melanin, followed by cells
simultaneously treated with melanin and LPS, and cells treated with after
is LPS stimulation ($p<0.05$ when compared to TNF-a production by
monocytes treated for 1 hour with melanin before stimulation with LPS).

Figure 9(A-C) shows that melanin strongly inhibits the TNF-(X
response in BALB/c mice. Circulating plasma concentrations of TNF-a
were measured by ELISA 90 min after i.v. injection. . . min before (19 mice);
simultaneously with (40 mice); or 15 min after (18 mice) LPS injection. The
concentrations of TNF-a in the melanin treated group and nontreated
controls (open bars) were compared by the two tailed Mann-Whitney Test
30 using the INSTATO 2.03 program. Results. . .

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,0, DETAILED DESCRIPTION OF TT-1E INVENTION

The present invention is broadly directed to the discovery that
melanin is useful for the therapeutic treatment of disease in animals,
5 including humans.

In one embodiment, the melanins used in the presently described
invention are substantially pure. In general, the term substantially pure
melanin shall refer to melanin preparations that are comprised of at least
about 75 percent of the desired melanin, specifically at least about 85 percent,
more specifically at least about 90 percent, and preferably at least about 95
weight percent.

As a consequence of normal melanin production, a wide variety of
protein and amino acid contaminants are typically incorporated into
naturally occurring melanins. Additionally, the wide variety of substrates
and contaminants that are typically available during normal melanin
production in vivo may lead to the production of melanins with
amorphous composition. Similarly, the wide variety of contaminants that
are typically found in commercially available preparations of tyrosinase, the
enzyme that makes melanin, are often incorporated into melanins
produced in vitro.

Where pharmaceutical applications of melanin are contemplated,
melanin products with defined and predictable compositions and structural
features are highly desirable, and may even be necessary. Additionally, the
contaminating proteins, and amino acids contained therein, that are often
incorporated into naturally occurring or previously described

melanins may
also prove immunogenic in the host. Thus, melanin preparations
that are
to be administered in vivo shall preferably be substantially free of
contaminating proteins, amino acids, and especially toxins of. . .

The term 'biosynthetic melanin shall refer to melanin
that is
.14 -
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produced by a recombinantly expressed and/or purified tyrosinase protein
that has been provided with a substrate for melanin
production. By
producing melanin using high specific activity tyrosinase in
conjunction
with defined substrates, melanins are produced with
substantially more
uniform structure and composition than melanins typically
found in
nature. With proper methods of synthesis, the resulting biosynthetic
melanins may also be substantially pure, or further processed
to produce
biosynthetic melanin preparations that are substantially pure.
In the
majority of instances, suitably processed biosynthetic melanin
may replace
10 naturally occurring melanin in any of the embodiments
described herein.

The purified or biosynthetic melanins used in the present
invention
may optionally be characterized by being substantially free of
contaminating
amino acid content. For the purposes of the present invention,. the term
substantially amino acid free shall refer to melanin
preparations that
15 generally contain less than about 10 percent amino acid content by
weight,
preferably less than about 7.5 percent amino. . . about 5 percent
amino acid content, and specifically less than 2.5
percent amino acid content by weight. Moreover,, compositions comprising
purified biosynthetic melanins shall generally be
substantially free of
20 potentially toxic contaminants of bacterial origin such as, but not
limited to,
bacterial endotoxins (particularly. . .

Where the therapeutic use of the presently described purified
melanins is contemplated, the purified melanin is
preferably administered
25 in a pharmaceutically acceptable carrier, via oral,, intranasal,.
rectal,, topical,,
intraperitoneal, intravenous,, intramuscular,, subcutaneous,, subdermal,
transdermal, intrathecal, or intracranial methods, and the like.
Typically,
the preferred formulation for the purified melanin will vary
depending
upon the region of the host requiring treatment.

For example, topical immune reactions are preferably treated or
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prevented by melanin formulations designed for topical
application,

whereas systemic reactions are preferably treated or prevented by administration of compositions formulated for parenteral administration.

Additionally, immune-mediated disorders of the pulmonary system may be treated both parenterally and by direct application of the therapeutic melanin compositions to the respiratory system by inhalation therapy.

Additionally, local immune reactions, i.e., arthritic or inflamed joints, etc., may be treated by localized injection purified melanin compositions into the synovial capsule. Optionally, such local administration of purified melanin compositions may be performed in conjunction with corticosteroids.

Additionally, the purified melanin may be loaded into lipid-associated structures (i.e., liposomes, or other lipidic complexes) which may enhance the pharmaceutical characteristics of the purified melanin. The lipid-melanin complex may subsequently be targeted to specific target cells by the incorporation of suitable targeting agents (i.e., specific antibodies or receptors) into the melanin/lipid complex. Optionally, the purified melanin may be directly complexed with a targeting agent to produce the desired effect.

Where melanin mediated treatment of inflammatory disorders of the digestive tract and alimentary canal are contemplated, lipid formulations (e.g., emulsions, n-dcroemulsions, liposomes, etc.) comprising purified melanin may significantly protect the melanin from the digestive process. Accordingly, melanin formulations are contemplated that may be orally administered. To the extent that additional enteric protection is desired, for added protection, it. . . -
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capsules (for example of soft or hard gelatin, which are themselves optionally additionally enteric coated. Alternatively, solid formulations comprising melanin may be treated more flexibly. They may either be coated with enteric materials to form tablets or they can be filled. .
.
. . .
Additionally, any of a variety of stabilizing agents may be utilized in

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conjunction with the described melanin compositions. Although the melanin itself may function as an antioxidant, the oxidation of melanin or other components of the described compositions may be substantially reduced by preparing formulations in accordance with the present invention under an inert. . .

Formulations comprising purified melanin may also be stabilized for

15 storage and shipment by any of a number of well established methods, including but not limited. . .

Where one seeks to augment long-term stability by freezing or freeze-drying
melanin compositions, suitable excipients may be added to the melanin
comprising preparations prior to freezing. Examples of such stabilizing
20 excipients include, mono or disaccharides (e.g., glucose, sucrose, etc.),,
polysaccharides, or any of. . .
. . .
the terms
treatment, therapeutic use, or medicinal use used herein shall refer to any and all methods of using the described purified melanin compositions to remedy a disease state or symptoms, or otherwise prevent,
30 hinder, retard, or reverse the progression of disease or any. . .

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undesirable symptoms in any way whatsoever. Similarly, a therapeutically effective amount of melanin is an amount sufficient to remedy a disease
state or symptoms, or otherwise prevent, hinder, retard, or reverse the progression of disease. . .
. . .
and interleukins including,
but not limited to, IL-1 and IL-6) production, in a particularly preferred
embodiment of the present invention, the purified melanin is used at a
dose that reduces or inhibits the excess production of TNF-cC while still
allowing or facilitating an effective host. . .

When used in the therapeutic treatment of disease, an appropriate dosage of purified melanin, or modified form thereof, may be determined
by any of several well established methodologies. For instance, animal studies are commonly used to. . .

The presently described purified melanins may also be complexed
with molecules that enhance their in vivo attributes. Examples of such molecules include, but are not limited to,. . .

Additionally, the purified melanins may be complexed with a variety
of well established compounds or structures that,, for instance, further enhance the in vivo stability of the melanin, or otherwise enhance its
15 pharmacological properties (e.g., increase in vivo half-life, reduce toxicity,
enhance solubility or uptake, etc.). Examples of such. . .

Where diagnostic, therapeutic or medicinal use of purified melanin,
20 or derivatives thereof, is contemplated, the melanin may generally be
prepared and maintained under sterile conditions that minin-Lize that risk
off or avoid, microbial contamination. Because of the relatively small size
and inherent stability of purified melanin, compositions

comprising
melanin may also be sterile filtered prior to use. In addition to the above
25 methods of sterile preparation and filter sterilization, antimicrobial agents
may also be added to the melanin compositions. Antimicrobial agents
which may be used, generally in amounts of up to about 3% w/v, preferably
from about 0.5 to 2.5%,. . . cresol, p-chloro-m-cresol, chlorobutanol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate and benzylalkonium chloride. Preferably, antimicrobial additives will either enhance the biochemical properties of
the melanin, or will be inert with respect melanin activity. To the extent
that a given antimicrobial agent may prove deleterious to melanin activity,
another agent may be substituted which effects the desired functions of
melanin to a lesser extent.

One embodiment of the presently claimed methods relates to the use of purified melanin to modulate the immune system. Such modulation is
deemed to be a function of melanin's ability to either directly or indirectly
effect cytokine expression or activity in vivo or in vitro. In a preferred
embodiment, the therapeutic use of melanin will downregulate cytokine
expression. Melanin's ability to downregulate cytokine expression may also
be exploited by using melanin in conjunction with established therapeutics
in order to reduce the severity of the adverse immune-related reactions associated with a given therapeutic. For example, IL-2 treatment has been
associated with adverse systemic consequences that are often dose dependent. Because of melanin's ability to modulate adverse immune
reactions, the use of melanin in conjunction with cytokine may allow for
the clinical use of higher systemic concentrations of cytokine. Accordingly,
an additional embodiment of the present invention is the use of purified
melanin to reduce the toxic side-effects of therapeutic agents.

. . .
adverse disease consequences have been linked with
25 excess TNF-(x production, in a particularly preferred embodiment of the
present invention, the purified melanin is used at a dose that reduces or
inhibits the excess production of TNF-cc while still allowing or facilitating
an effective host. . .

Given that melanin is useful for treating the wasting syndrome that
is often associated with acquired immunodeficiency syndrome (AIDS), or
cancer, the presently described methods. . .

An additional embodiment of the present invention is the use of
purified melanin to treat allergy related hypersensitivity

reactions.

Particularly contemplated is the use of purified melanin to prophylactically
treat individuals that may be susceptible to the adverse consequences of allergic reactions such as, but not limited to, drug reactions, insect stings,,
dermatitis,, food allergies,, and the like. Additionally contemplated is the
intervening use of purified melanin to alleviate or reduce the adverse
symptoms of allergic reactions.

Melanin is a virulence factor that contributes to the pathogenesis of a
variety of infectious agents. To the extent that melanins that are
30 characteristic of a particular pathogen may be identified, an additional aspect

of the presently claimed invention is the use of purified melanin, or
portions or analogues thereof, as vaccines to prevent progression and spread of melanin producing pathogens.

Similarly, the identification and use of melanoma associated or specific melanins is contemplated to provide an additional form of cancer
therapy comprising the use of tumor specific melanins, or fragments or
analogues thereof, as cancer vaccines, or tumor-specific immunostimulants.

Additionally, the identification of pathogen or tumor specific melanins shall be useful for the identification or production of receptors,
ligands, or polyclonal or monoclonal antibodies that specifically bind to the
pathogen or tumor specific melanin. Accordingly, an additional embodiment of the present invention are receptor, ligand, or antibody-
based diagnostics or therapeutics that target pathogen or tumor specific melanins, or the cellular receptors therefore.

6 Synthesis of Water-Soluble Melanin
Water soluble melanin was produced and prepared for use essentially
as described in U.S. Patent Nos. 5,340,734; 5,466,592; 5,486,351; 5,210,076 and
25 5,057,325 herein incorporated by reference. Melanins produced using the
described methods were further purified by acid precipitation by addition of
concentrated HO]pH 1 Precipitated melanin was recovered by centrifugation.

When analyzed for purity, the resulting melanin (designated AHM 8)
30 was found to comprise about 96% percent of the final product by weight.

The amino add content of melanin AHM 8 was less than 4.2%. The total amino add was 8.4% by weight of which 4.38% was tyr + gly. The elemental analysis yielded the following: %C=51.01; %H=3.74; %N=9.5; %S=O; and %0=33

The endotoxin content of melanin AHM 8 was estimated using the chromogenic Limulus amebocyte lysate (CLAL) test kit (BioWhittaker, Inc., Walkersville, MD). To determine whether AHM 8. . . content of the mixture was determined using the CLAL test according to the manufacturer's directions. Percent reduction in the endotoxin content of melanin-containing standard preparation was calculated as follows.

. . .

gg/ml AHM 8

produced 22% reduction in the activity of the endotoxin standard. As shown in Table 1, the endotoxin content of melanin AHM 8, at 50]tg/ml, was only 0.069 endotoxin unit (EU)/ml. Under our experimental conditions, the production of TNF-a by'human peripheral blood. . .

6,2, Pretreatment With Melanin Suppresses LPS-Induced TNF-cc Production

The effect of biosynthetic melanin on in vitro TNF-(x production was 25 evaluated by comparing the levels TNF-(x in the culture supernatants of melanin-treated and nontreated monocytes following stimulation with LPS. In these experiments, monocytes, (1 X 106/Ml), were incubated with various doses of melanin at 37'C in a humidified atmosphere containing 30 5% C02. Following a 30-60 min incubation, monocytes were stimulated

with LPS in the continuous presence of melanin. Controls included (1) melanin-nontreated cells stimulated with LPS; (2) melanin-treated, LPS-nonstimulated monocytes; and (3) monocytes incubated in complete medium in the absence of additives. Twenty-four hours after stimulation with LPS, the levels. . .

As shown in Figure 1, treatment of monocytes with melanin AHM 8 resulted in a dose-dependent inhibition of LPS-induced TNF-a production.

To ensure that the presence of melanin in the culture supernatants did not interfere with the assay (ELISA), the TNF-a concentrations in the supernatants collected from melanin-treated monocytes were determined from two standard curves. For construction of the control standard curve, TNF-a standards were diluted in complete culture medium. . .

Melanin-containing standard curves were constructed by plotting optical density (O.D.) values obtained from TNF-(x standards (over a range from 0 to 1,000 pg/ml) that were diluted in complete medium incubated with 0-50 4g/ml melanin for 24 hours at VC. In parallel assays, the TNF-a content of

culture supernatants collected from monocytes that were treated with 0-50
gg/ml melanin before stimulation with LPS (referred to hereafter as the test
samples) were determined by reading their O.D. against each standard
30 curve.. . .

As shown in Table 3, SI values of supernatants collected from
melanin-pretreated monocytes were consistently lower than the SI values
of supernatants collected from cells were not exposed to melanin . Taken
10 together, these data indicate that melanin suppresses LPS-induced TNF-a
synthesis/release by human monocytes and that this reduction is not the
consequence of an inhibitory effect of melanin on the assay system.

TABLE3
is INFLUENCE OF MELANIN ON TNF-a-SPECIFIC ELISA'
Melanin TNF-oc Content of Culture Supernatants
Content of from Cells Treated with AHM 8 (gg/ml)
TNF-(x
Standard
0 10 25 50
(Stimul
ation
Indexl
78
39 17 7
69
35 16 7
82. . .

63* The Effect of Melanin on Protein Synthesis by Human Peripheral Blood Monocytes
To determine whether melanin selectively interferes with the production of LPS-induced cytokines, the effect of melanin AHM 8 on
constitutive protein synthesis by human monocytes was measured. Protein synthesis was measured by incorporation of ['H]leucine. Monocyte protein
10 synthesis after 5 hours incubation in the presence of 100 [tg/ml melanin
AHN4 8 was roughly comparable to that displayed by melanin nontreated
control cells (23% lower). Under parallel experimental conditions incubation of monocytes with 20 4g/ml cycloheximide resulted in complete is inhibition of ['H]-leucine. . .
. . .
incorporation in monocytes incubated for
20 20 hours in the presence of 100gg/ml AHM 8 was also comparable to that of
the melanin nontreated cells (32,775 ±1,977 cpm versus 29,713 ±856 cpm).

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Melanin Selectively Suppresses Cytokine Production by Human Monocytes
To determine whether melanin suppresses the production and release of other LPS-induced cytokines, peripheral blood monocytes were tested (essentially as described above) for the ability to produce TNF-a, IL-19,
IL-6 and granulocyte/macrophage-colony stimulating factor (GM-CSF) after melanin treatment. The levels of TNF-(x, IL-19, and GM-CSF in

the culture
supernatants were measured, in duplicate, using ELISA kits purchased from
Biosource. . .
. . .
with AHM 8 produced significantly ($p < 0.05$) lower
levels of TNF-cc, IL-1p, and IL-6 than did their respective controls. Under
parallel conditions, melanin did not inhibit production or release of GM-
CSF by LPS stimulated monocytes. In contrast, monocytes pretreated with
30 100 gg AHM. . . SHEET (RULE 26)
following stimulation with LPS ($p < 0.01$). This indicates that AEM 8 does not inhibit LPS signalling. The finding that melanin does not suppress GM-
CSF secretion is of particular interest. GM-CSF affects the intracellular
phosphorylation of nucleoside analogues in monocytes and macrophages,
5. . .

6,5, Continuous Presence of Melanin Is Not Required for S of TNF-a Production

To determine whether suppression of TNF-a production requires the continuous presence of melanin, freshly isolated human monocytes (jX106
cells/ml of complete medium) were treated with inhibitory concentrations of melanin AHM 8. Following a 1 hr incubation at 37'C, monocytes in one
set of culture were stimulated with LPS in the continuous presence of is melanin. Monocytes in a second set of cultures were washed once by low-
speed centrifugation before stimulation with LPS. Controls included (1) melanin-nontreated cells stimulated with LPS; (2) melanin-treated, LPS-
nonstimulated monocytes; and (3) monocytes incubated in complete medium in the absence of additives. Twenty-four hours after stimulation
20 with LPS, the levels of TNF-a in the culture supernatants were measured in
duplicate, by ELISA. Suppression of TNF-cc production did not require that melanin be continuously present. In fact, TNF-(x production was
suppressed by 63% even after the melanin had been washed out of the
25 culture immediately before stimulation with LPS (data not shown).

*6, Melanin-Mediated Suppression of TNF-a Production Is Reversible

To allow time for recovery, monocytes pretreated with the inhibitory concentrations of melanin AHM 8 were incubated for 2-18 hours in
complete medium before stimulation with LPS. For each time point, the following cultures served as control: (1) melanin-nontreated, LPS-
stimulated; (2) melanin-nontreated, LPS-nonstimulated; and (3) melanin-
treated, LPS-nonstimulated monocytes. The concentration of TNF-(x in the culture supernatants was measured 24 hours after the addition of LPS.

Data from two experiments, shown in Figure 3(A & B), demonstrate that melanin-mediated suppression of TNF-a persisted at least for 7 hours.

The suppressive effects of melanin were reversed upon short-term culture.

Monocytes stimulated with LPS 18 hours after removal of melanin exhibited a higher TNF-oc response (44-47% decrease in TNF-(X release versus a 74-88% reduction after a 7-hour AHM 8 washout period). These data indicate that monocytes treated with 100 gg melanin AHM 8/ml were not killed under these experimental conditions and that recovery from melanin-mediated suppression is time-dependent.

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,7* Melanin Suppresses Production of TNF-(x by Activated Monocytes

The data presented in the preceding sections are from experiments in which monocytes were pretreated with melanin AHM 8 before LPS stimulation. To determine whether melanin suppresses production of TNF-a even when it is administered after LPS-stimulation, monocytes were treated with melanin either 1 hour after, simultaneously with, or 1 hour before stimulation with LPS. As expected, melanin added 1 hour before LPS drastically inhibited LPS-induced TNF-(x production (84 ±4% inhibition at 10 100]ig/ml) (Figure 4). When melanin was added 1 hour after LPS stimulation, a partial suppression of TNF-cc response was observed (45 ±13% inhibition at 100]tg/ml, p=0.05). Melanin added at earlier time points following LPS stimulation did not exert a stronger suppressive effect.

15 Treatment of monocytes with 100 gg/ml melanin either 7.5 or 60 min after LPS stimulation reduced TNF-a production by 50% and 52%, respectively (not shown). These data indicate that melanin may provide a corrective benefit as well as a preventative benefit, and may also indicate that at least 20 two separate mechanisms are responsible for the net reduction in TNF-(x production seen after prior exposure to melanin.

The finding that melanin appears less effective at suppressing TNF-(x secretion by activated monocytes is of particular interest because this cytokine is an essential mediator in the immune response. This finding 25 suggests that melanin could be used to reestablish a balanced or normal level of TNF-a in patients with wasting syndrome without destroying the patient's ability. . .

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,8, Effect of Melanin on TNF-a Production Induced by Additional Stimuli

To test whether AHM 8 has the ability to modulate TNF-a production by cells that have. . .

6e9 Effect of melanin on the expression of TNF-a mRNA

Northern blot hybridization (Chomczynski and Sacchi, Anal.

6 Effect of Melanin on TNF-a PrQduction In Vivo

To determine whether melanin reduces cytokine production in vivo,
circulating concentrations of TNF-(x were measured in mice that had been
.37 -
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injected with. . .
. . .
1987). Therefore, the in vivo TNF-(x response to LPS was used as a model to determine the cytokine regulatory effects of melanin.
. . .
(0.625 mg/Kg) and 50 mg
20 AHM 8/Kg body weight (Acute toxicity studies showed that a single Lv. dose
of 5 g/kg melanin was well tolerated by Sprague Dawley rats). Control mice
received either LPS, AHM 8, or PBS. A PBS sham injection was. . .

Results from two subsequent experiments showed that plasma TNF-a levels in mice injected with 50 mg/kg melanin 60 min before challenge
with LPS was 77% lower than those injected with LPS alone (Figure 9A, p <
15 0.001). The concentration of TNF-a in the plasma of 10 mice given either
melanin alone or PBS (the vehicle) was 33 ±16 and 45 ±17 pg/ml,
respectively.
. . .
62% (n = 40) when mice were injected concomitantly with LPS and 50 mg/Kg AHM 8 (Figure 9B, p < 0.0001). Melanin was also inhibitory at 25
mg/Kg. The plasma TNF-(x concentration in 12 mice injected concomitantly with 0.625 mg/Kg LPS and 25 mg/kg. . . 4,473 ± 1,913
23 pg/ml, p = 0.05). The inhibitory effect exerted by AHM 8 was not due to
direct interaction of melanin with LPS because in these experiments mice
were first injected in one tail vein with LPS and immediately into a second
tail. . .

Melanin was also effective when administered 15 min after LPS
30 challenge. As shown in Figure 9C, the levels of circulating TNF-(x in mice
- 39 -
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injected with melanin 15 min after LPS administration was significantly (p
= 0.008) lower than the corresponding controls injected with LPS alone.

However, melanin was incapable of down regulating TNF-(x production/release when injected 30 min after LPS insult (data not shown).
. . .
in mice (Garina et al. J. Exp. Med. IM:1305-1310,1991), and suggest that once the posttranscriptional phase of TNF-a biosynthesis
has been completed, melanin is incapable of downregulating the process.

Taken together these data indicate that melanin significantly reduces

TNF-a production/release under acute inflammatory condition and that there is no need for pretreating the animals to achieve the protective effect
of melanin.
. . .
have been specifically exemplified in the above in
15 vivo studies, typically, any acceptable animal model may be used to assess
purified melanin's ability to modulate cytokine expression in vivo.
. . .
and the mode
of injection. Accordingly, the following disclosure provides an example of
20 an in vivo study where prior treatment with melanin provides prophylactic
protection against subsequent challenge with endotoxin. The following example is provided solely for purposes of exemplification and should not
be deemed. . .

Purified melanin (AHM 8) is usually injected i.v. and is generally
- 40 w
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introduced into test animals at a concentrations. . .

Following melanin treatment, the various control and test subjects
are injected with a variety of sub-lethal and lethal doses of mitogen (LPS, or
other. . . systemic sepsis or
shock). Blood samples are drawn at suitable time intervals after introduction in order to quantify the amounts of purified melanin and
10 cytokine that are present in the bloodstream. Alternatively, where lethal
doses of mitogen are used, the extent to which melanin confers protection
to the test animals is determined.

CLMEN 1 A method of modulating cytokine production by an animal cell, comprising: administering purified melanin to said cell in an amount
sufficient to modulate cytokine production by said cell.

8 A method of modulating cytokine production by an animal, comprising administering purified melanin to said animal in an amount sufficient to
alleviate or reduce an adverse symptom of a disease associated with cytokine expression.

18 A method of reducing the systemic toxicity of a therapeutic agent comprising administering purified melanin to an individual in an amount
sufficient to reduce or alleviate an adverse symptom associated with said
20 therapeutic agent.
- 43 -
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DETD    Similarly, the identification and use of melanoma associated
        or
        specific melanins is contemplated to provide an additional form of
        cancer
        therapy comprising the use of tumor specific melanins, or.  .  .


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---Logging off of STN---



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Executing the logoff script...


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COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 8.23       8.44

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